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FILE COVERS 1971 TO PATENT PUBLICATION DATE: 23 Jul 2002 (20020723/PD)
FILE LAST UPDATED: 23 Jul 2002 (20020723/ED)
HIGHEST GRANTED PATENT NUMBER: US6425133
HIGHEST APPLICATION PUBLICATION NUMBER: US2002095707
CA INDEXING IS CURRENT THROUGH 23 Jul 2002 (20020723/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 23 Jul 2002 (20020723/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2002
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Jun 2002

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>>>  classifications, or claims, that may potentially change from      <<<
>>>  the earliest to the latest publication.                           <<<

This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> s pioglitazone and breast cancer
           328 PIOGLITAZONE
         21835 BREAST
         49970 CANCER
          8023 BREAST CANCER
                 (BREAST(W)CANCER)
L1          42 PIOGLITAZONE AND BREAST CANCER

=> s l1 and pd<1999
       2432884 PD<1999
                 (PD<19990000)
L2           4 L1 AND PD<1999

=> d l2 1-4 bib, ab, kwic
```

L2 ANSWER 1 OF 4 USPATFULL
AN 2001:82522 USPATFULL
TI Methods and pharmaceutical compositions for inhibiting tumor cell growth
IN Spiegelman, Bruce M., Waban, MA, United States
Altiok, Soner, Cambridge, MA, United States
Mueller, Elisabetta, Boston, MA, United States
Sarraf, Pasha, Boston, MA, United States
Tontonoz, Peter, San Diego, CA, United States
PA Dana-Farber Cancer Institute, Boston, MA, United States (U.S. corporation)
PI US 6242196 B1 20010605
WO 9825598 19980618 <--
AI US 1999-319769 19990917 (9)
WO 1997-US22879 19971211
19990917 PCT 371 date
19990917 PCT 102(e) date
DT Utility
FS Granted
EXNAM Primary Examiner: Leary, Louise N.
LREP Lahive & Cockfield, LLP, Mandragouras, Amy E., Smith, DeAnn F.
CLMN Number of Claims: 35
ECL Exemplary Claim: 1
DRWN 36 Drawing Figure(s); 24 Drawing Page(s)
LN.CNT 2761
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method for inhibiting proliferation of a PPAR .gamma.-responsive hyperproliferative cell which comprises the step of contacting the cell with (I) an inhibitory amount of a PPAR.gamma. agonist and (II) a MAP kinase inhibitor is disclosed. A method for treating or prophylactically preventing in an animal subject a disorder characterized by unwanted proliferation of PPAR.gamma.-responsive hyperproliferative cells which comprises administering to the subject (I) an inhibitory amount of a PPAR.gamma. agonist and (II) a MAP kinase inhibitor is also disclosed. Pharmaceutical compositions comprising a therapeutically effective amount of a PPAR.gamma. agonist and a MAP kinase inhibitor are disclosed for use in the methods.
PI US 6242196 B1 20010605
WO 9825598 19980618 <--
SUMM . . . myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, **breast cancer**, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary. . .
SUMM . . . the PPAR.gamma. protein. For example, the PPAR.gamma. agonist can be a thiazolidinedione, or an analog thereof. Exemplary PPAR.gamma. agonists include **pioglitazone**, troglitazone, ciglitazone, englitazone, BRL49653, and chemical derivatives thereof. In certain preferred embodiments, the PPAR.gamma. agonist is represented in the general. . .
SUMM . . . metastatic breast tumors. Accordingly, another aspect of the present invention provides a method for diagnosing or augmenting the diagnosis of **breast cancer**, comprising detecting in a sample of transformed cells one or both of a diagnostic level of PPAR.gamma. mRNA or PPAR.gamma.. . .
DRWD FIG. 1 is a panel of photographs showing the effects of **pioglitazone** in stimulating growth arrest and adipose differentiation of NIH-3T3 cells ectopically expressing PPAR.gamma.

(NIH-PPAR.gamma.) compared to control cells infected with. . .

DRWD . . . of PPAR.gamma. ligands. FIG. 2A is a graph depicting the cumulative growth of cells untreated or treated with 5 .mu.M **pioglitazone**. FIG. 2B is a bar graph showing the percent decrease in cell number in the **pioglitazone**-treated plates relative to the untreated plates. FIG. 2C is a bar graph showing exponentially growing cells treated without or with two thiazolidinediones, **pioglitazone** (5 .mu.M) or BRL49653 (1 .mu.M) for 5 days.

DRWD . . . shows schematic representations of wild type PPAR.gamma.1 and 2, or mutant PPAR.gamma.2 cDNAs. The right panel shows the effects of **pioglitazone** treatment on the growth rate of cells expressing wild type or mutant forms of PPAR.gamma. treated with or without **pioglitazone**.

DRWD . . . level of activation is indicated with respect to the concentration of the thiazolidinedione compounds, BRL 49653 (shown by filled circles), **pioglitazone** (shown by unfilled circles) and troglitazone (shown by filled squares).

DRWD . . . of liposarcoma cells cultured in the absence (panels A, C and E) and in the presence of the PPAR.gamma. ligand **pioglitazone** (panels B, D and F). Panels A and B represent untreated and treated cells, respectively; panels C and D represent. . .

DRWD . . . from a retroviral vector (NIH-PPAR.gamma.) and human liposarcoma cells (LS 857). Indicated are untreated cultures (-) and cultures treated with **pioglitazone** alone (pio), the RXR-specific ligand, LG 268, or both. As indicated to the left, the blot was hybridized with PPAR.gamma.,. . .

DRWD . . . treatment of RXR-or PPAR.gamma.-specific ligands on primary cultures of human liposarcoma cells (LS 857) with the indicated ligands: LG 268, **pioglitazone** (pio), both ligands (pio and LG 268), BRL 49653 alone (BRL), or in combination with LG 268 (BRL and LG. . .

DRWD FIGS. 12 and 13 are graphs depicting the effect of LG 268 ("1g") and **pioglitazone** ("pio") on the HL-60 (leukemic) cell line.

DRWD FIG. 14 is a graph depicting the effect of LG 268 ("compound 268") and **pioglitazone** ("pio") on the human prostrate cancer cell line PC3.

DRWD FIG. 15 is a Northern analysis demonstrating the PPAR.gamma. mRNA expression in **breast cancer** cell lines and tumors. Northern blot analysis of breast cell lines and tumors was performed with 30 .mu.g of total. . .

DRWD FIG. 16 shows immunocytochemical staining of metastatic **breast cancer** and normal breast tissue with antibody against PPAR.gamma.. Consecutive sections were stained either with heamatoxilin and eosin or with PPAR.gamma.. . .

DRWD FIG. 17 shows lipid accumulation in **breast cancer** cells induced by PPAR.gamma. ligands. Staining for lipids was performed with Oil red O (a,c) or by Nile Red fluorescent. . . Neutral lipid stains with Oil Red O and yellow with Nile Rad. a. 21PT cells were treated with 10 .mu.M **pioglitazone** or troglitazone or vehicle for 7 days. b. 21PT cells were treated with 10 .mu.M M2 compound, an inactive metabolite. . . 10 .mu.M troglitazone or 5 .mu.M 15 deoxy.DELTA. .sup.12,14 PGJ.sub.2 for 5 days. C. 21MT cells treated with 10 .mu.M **pioglitazone**, troglitazone or vehicle for 15 days.

DRWD FIG. 18 shows the effects of PPAR.gamma. activation on growth and gene expression of 21PT **breast cancer** cells. (a) Northern blot analysis of RNA from 21PT cells treated for 7 days in with **pioglitazone** (10 .mu.M), LG268 (100 nM) or with the combination of **pioglitazone** and IG268, or vehicle alone. 30 .mu.g of total RNA were loaded per lane. (b) Incorporation of thymidine in cells that were exponentially growing, when exposed to 10 .mu.M

pioglitazone or troglitazone for 3 or 7 days. Cells were then incubated with 2.mu. Ci/ml of .sup.3 H-thymidine for a further 24 hours with troglitazone, **pioglitazone** or vehicle. Error bars represent the standard deviation. (c) Clonogenic assay in cells treated first with troglitazone or vehicle for. . .

DETD Cancer of the breast accounts for more deaths among American women than any other malignancy. Current therapy for primary **breast cancer** includes surgical resection with or without radiation or chemotherapy depending on the extent of the disease. Conventional adjuvant chemotherapy is. . . two major reasons: it is associated with significant toxicity and it may benefit only 20-25% of patients. For advanced metastatic **breast cancer** standard cytotoxic chemotherapy is mainly palliative causing only slight improvement in survival rate.

DETD . . . is shown to be expressed consistently in each of the major histologic types of human liposarcoma, and in adenocarcinomas from **breast cancer** cells. Activation of this receptor with ectopically added receptor ligand is shown to promote terminal differentiation of primary liposarcoma cells. . .

DETD . . . genes which contain a PPAR.gamma. responsive element. Examples of such ligands include, but are not limited to thiazolidinedione compounds, e.g., **pioglitazone**, troglitazone, BRL49653, and derivatives thereof, or prostaglandin (PG) metabolites, e.g., prostaglandin 15-deoxy-.sup..DELTA.12,14 PGJ.sub.2, and derivatives thereof.

DETD . . . myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, **breast cancer**, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary. . .

DETD Exemplary PPAR.gamma. agonist can be selected from amongst such compounds as 5-[4-[2-(5-ethylpyridin-2-yl)ethoxyl]benzylithiadiazolidine-2,4-dione: (**pioglitazone**); 5-[4-[(1-methylcyclohexyl)methoxy]benzyl]thiadiazolidine-2,4-dione: (ciglitazone); 5-[(2-benzyl-2,3-dihydrobenzopyran)-5-ylmethyl]thiadiazoline-2,4-dione: (englitazone); 5-[(2-alkoxy-5-pyridyl)methyl]-2,4-thiazolidinedione; 5-[(substituted-3-pyridyl)methyl]-2,4-thiazolidinedione; 5-[4-(2-methyl-2-phenylpropoxy)benzyl]thiazolidine-2,4-dione; 5-[4-[3-(4-methoxyphenyl)-2-oxooxazolidin-5-yl]-methoxy]benzyl-2,4-thiazoli-dinedione; 5-[4-[3-(3,4-difluorophenyl)-2-oxooxazolidin-5-yl]-methoxy]benzyl-2,4-thiazo-lidinedione; 5-[4-[3-(4-chloro-2-fluorophenyl)-2-oxooxazolidin-5-yl]methoxy]benzyl-2,4-thiazolidinedione; 5-[4-[3-(4-trifluoromethoxyphenyl)-2-oxooxazolidin-5-yl]methoxy]benzyl-2,4-thiazolidinedione; 5-[4-[3-(4-trifluoromethylphenyl)-2-oxooxazolidin-5-yl]methoxy]benzyl-2,4-thiazolidinedione; 5-[4-[2-[3-(4-trifluoromethylphenyl)-2-oxooxazolidin-5-yl]ethoxy]benzyl]-2,4-thiazolidinedione; 5-[4-[2-[3-(4-chloro-2-fluorophenyl)-2-oxooxazolidin-5-yl]ethoxy]benzyl]-2,4-thiazolidinedione; 5-[4-[3-(4-pyridyl)-2-oxooxazolidin-5-yl]methoxy]-benzyl-2,4-thiazolidinedione; 5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione: (troglitazone); 4-(2-naphthylmethyl)-1,2,3,5-oxathiadiazole-2-oxide; 5-[4-[2-N-(benzoxazol-2-yl)-N-methylamino]ethoxy]benzyl]-5-methylthiazolidine-2,4-dione; 5-[4-[2-[2,4-dioxo-5-phenylthiazolidin-3-yl)ethoxy]benzyl]thiazolidine-2,4-dione;. . .

DETD . . . yet another aspect, detection of PPAR.gamma. RNA and/or protein

expression can provide a useful diagnostic method for detecting and/or phenotyping **breast cancer** cell disorders. For example, as described in the appended examples, PPAR.gamma. is found to be expressed at significant levels in. . . the TZD ligand sensitivity of relatively non-responsive cells, suggesting that this enzyme can interfere with the function of PPAR.gamma., in **breast cancer** cells.

DETD . . . of PPAR.gamma. cDNA as well as HIB1B and 3T3-F442A cell lines were cultured in DMEM containing 10% cosmic calf serum. **Pioglitazone** (5-[4-[2-(5-ethyl-2-pyridyl)-ethoxy]benzyl]-2,4-thiazolidinedione) (Upjohn), was dissolved in DMSO and used in cell culture experiments.

DETD Exponentially growing NIH-PPAR.gamma. and NIH-vector cells were treated with a synthetic PPAR.gamma. ligand **pioglitazone**, which belongs to the class of thiazolidinedione antidiabetic agents (Lehmann, J. M. et al. (1995) J. Biol. Chem. 270:12953-6). After selection in puromycin, cells were pooled and cultured with or without **pioglitazone** (5 .mu.M) for 5 days. As shown in FIG. 1, treatment with **pioglitazone** at 5 .mu.M concentration bad no obvious effect on cells containing empty vectors. In contrast, this agent had dramatic effects. . .

DETD Time course studies at different time points after **pioglitazone** treatment showed that the number of NIH-PPAR.gamma. cells in ligand-treated plates was reduced by almost 40% relative to controls by 2 days after treatment and by 80% after 5 days with **pioglitazone** (FIGS. 2A, B). The same number of NIH-PPAR.gamma., NIH-vector or HIB1B cells were cultured either in the presence (+) or. . . is represented as percentage decrease in cell numbers in the treated plates relative to untreated control plates. The growth of **pioglitazone** treated NIH-vector cells decreased by 10% over this period compared to untreated control cells, which may be due to the. . .

DETD To analyze whether **pioglitazone** treatment of cells expressing PPAR.gamma. affects progression through a specific cell cycle stage we performed fluorescence activated cell sorting (FACS). . . the G0/G1 phase of cell cycle (data not shown). The percentage of cells undergoing DNA synthesis after 5 days of **pioglitazone** treatment was determined by the ability of cells to incorporate BrdU. As shown in table 1, ligand treatment did not. . . rapidly proliferating cells. Specifically shown in table 1 are cells cultured on coverslips were untreated or treated with 5 .mu.M **pioglitazone** for 5 days and then pulsed with BrdU for 1 hour. Coverslips were fixed and processed as described in materials. . .

DETD

	pioglitazone	BrdU positive %
NIH-vector	-	44
NIH-vector	+	43
NIH-PPAR.gamma.	-	44
NIH-PPAR.gamma.	+	9
HIB1B	-	75
HIB1B	+. . .	

DETD . . . vectors containing wild type or various mutant forms of PPAR.gamma. cDNA. Exponentially growing cells were treated for 5 days with **pioglitazone** and cell numbers were determined. As shown in FIG. 3, ligand activation of both PPAR.gamma.1 and PPAR.gamma.2 induced a similar. . . changed to serine; NIH-CD cells express a truncated form of PPAR.gamma.2 which lacks the conserved carboxyl terminal transactivation domain. Thus, **pioglitazone** treatment did not have any affect on cell growth and adipogenesis in NIH-M2 and NIH-CD cells. Treatment with **pioglitazone** caused about a 10% decrease in cell growth in NIH-vector cells. Cell numbers were determined after 5 days treatment without or with 5 .mu.M

pioglitazone. Decrease in the cell number in treated plates was represented as relative change to untreated control plates. The data represent. . .

DETD . . . adipocyte specific aP2 promoter (Ross, S. R. et al. (1992) PNAS USA 89:7561-5). Exponentially growing HIB1B cells were treated with **pioglitazone**, cell numbers were determined and BrdU incorporation experiments were performed to evaluate the effect of PPAR.gamma. activation on cell cycle progression. As shown in FIGS. 2A, 2C and FIG. 3, PPAR.gamma. activation by **pioglitazone** or BRL49653 strongly repressed the growth of these cells. BrdU incorporation into newly synthesized DNA was also decreased 85% after 5 days of treatment with **pioglitazone** (Table 1). These results show that PPAR.gamma. activation can overcome SV40LT driven transformation and cause cell cycle withdrawal in HIB1B. . .

DETD . . . 2.times.10.sup.5 cells/ml and cultured in 60 mm dishes in RPMI containing 15% Cosmic Calf Serum (Hyclone) and 5 .mu./ml insulin. **Pioglitazone** (Upjohn), troglitazone (Warner-Lambert), BRL49653 (BIOMOL) and LG268 (Ligand Pharmaceuticals) were dissolved in DMSO and applied to cells in a volume. . .

DETD . . . identified as ligand activators of the murine homologue of PPAR.gamma.. As shown in FIG. 6, the thiazolidinediones BRL49653, troglitazone and **pioglitazone** are effective activators of human PPAR.gamma., and their relative potency parallels their potency as insulin-sensitizing agents in vivo (BRL>troglitazone> **pioglitazone**).

DETD . . . of stainable lipid under these conditions. When cultures were treated for 7 days with 10 .mu.M of the PPAR ligand **pioglitazone**, the cells readily accumulated lipid and adopted a morphology characteristic of mature cultured adipocytes (FIG. 7). No lipid accumulation was. . . to 75% in the LS175 cells. After induction for 7 days with thiazolidinedione, cells maintained their differentiated morphology even when **pioglitazone** was withdrawn. This experiment was performed at least twice with each cell strain with quantitatively and qualitatively similar results. Induction. . .

DETD . . . LG268 resulted in significant stimulation of adipocyte differentiation, comparable to that seen with 7 days of treatment with 1 .mu.M **pioglitazone** alone. Simultaneous exposure to both activators resulted in an additive effect. LG268 had no effect on NIH-vector cells, indicating that the adipogenic activity of this compound, like that of **pioglitazone**, is dependent on the presence of PPAR.gamma.. Similar results were obtained with the preadipocyte cell lines 3T3-L1 and 3T3-F442A which express both PPAR.gamma. and RXR.alpha. (data not shown). Northern analysis confirmed that **pioglitazone** and LG268 had an additive effect on the induction of the adipocyte-specific genes aP2 and adipsin in NIH-PPAR.gamma. cells (FIG.. . .

DETD . . . (NIH-vector) or NIH cells that express PPAR.gamma. from a retroviral vector (NIH-PPAR.gamma.) cultured in the absence or the presence of **pioglitazone** alone, LG268 alone, or in combination. Extent of adipocytic differentiation is indicated as the percentage of lipid-containing cells.

DETD

cell line	no activator	+**pioglitazone**	+LG268	**+pioglitazone** + LG268
NIH-vector	0	0	0	<1
NIH-PPAR.gamma.	2-5	60-70	50-65	>90

DETD . . . cells with 50 nM LG268 led to a significant degree of adipocyte differentiation, similar to that seen with 10 .mu.M **pioglitazone** alone. When LS857 cells were treated simultaneously with LG268 and a thiazolidinedione (either **pioglitazone** or BRL49653) an additive effect on differentiation was observed. To further characterize

the effects of PPAR.gamma. and RXR ligands on. . . the tumor from which they were derived, express PPAR.gamma. mRNA (c.f. FIG. 5A, tumor 204SP). Treatment of LS857 cells with **pioglitazone** leads to the induction of two markers of terminal adipocyte differentiation, the mRNAs encoding aP2 and adipsin (FIG. 8). Simultaneous treatment with **pioglitazone** and LG268 results in an additive induction of adipocyte gene expression. In summary, treatment of LS857 cells with thiazolidinediones and. . .

DETD . . . cells is accompanied by growth arrest. To address this issue, LS857 cells were cultured in the presence or absence of **pioglitazone**. Following induction of morphologic differentiation, **pioglitazone** was withdrawn. After 48 hours of continued culture in the absence of **pioglitazone**, cells were labeled for 48 hours with bromodeoxyuridine (BrdU). Cells undergoing DNA synthesis during the labeling period should stain positive. . .

DETD Table 4: Effects of **pioglitazone** in inducing growth arrest of primary cultures of human liposarcoma cells (LS 857) in the presence or the absence of **pioglitazone**. Extent of adipocytic differentiation is indicated as the percentage of lipid containing cells. Degree of proliferation is indicated by the. . .

DETD . . . HL-60 cells were plated at 5000 cells/well in 24 well plates and treated with varying concentrations of LG 268 and **pioglitazone**. After 5 days, aliquots were removed and used to measure cell number via coulter counter. The values provided in the. . .

DETD . . . growing phase were placed in 24 well plates at 5000 cells/well and treated with varying concentrations of LG 268 and **pioglitazone**. After 5 days, the cells were assessed for granulocytic/monocytic differentiation via the NBT assay. Higer levels of conversion of NBT. . .

DETD FIG. 14 is a graph depicting the effect of LG 268 ("compound 268") and **pioglitazone** ("pio") on the human prostrate cancer cell line PC3. Briefly, PC3 cells were plated at 2000 cells/well in 96 well plated and treated with varying concentratios of LG 268 and **pioglitazone**. After 5 days, viability was assed by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium-bromide (MTT) assay in order to determine the degree of drug-induced inhibition.. . .

DETD Terminal Differentiation of Human **Breast Cancer**: Expression and Ligand Activation of PPAR.gamma.

DETD **Pioglitazone** was provided by Upjohn Co, Kalmazoo, Mich. Troglitazone and PD147275 (M2) were obtained from Parke-Davies/Warner-Lambert, Ann Arbor, Mich. 15-deoxy-.DELTA..sup.12,14 -prostaglandin. . .

DETD . . . from the primary tumor, whereas the 21MT cells were derived from a pleural effusion when this same patient relapsed with **breast cancer** metastatic to the lung. While both the primary and metastatic breast cell lines express PPAR.gamma., the 21MT cells express the. . .

DETD . . . (arrow 3) as well as adjacent normal fat cells (arrow 4) (FIGS. 16c-d). Preimmune sera showed no nuclear staining of **breast cancer**, normal breast tissue, adipocytes or lung pneumocytes (data not shown).

DETD . . . 21PT and 21MT cells discussed above. When the 21PT cells were treated for 7 days with two different PPAR.gamma. ligands, **pioglitazone** and troglitazone, the cells underwent a morphological conversion, rounding up and filling with neutral lipid that stained with Oil Red. . .

DETD These data suggest a remarkable cellular response in some **breast cancer** cells to the TZDs. To confirm that this response is the result of PPAR.gamma. activation, we used another ligand for. . .

PPAR.gamma. can stimulate a dramatic morphological conversion and lipid accumulation in a malignant breast cell line However, at least one **breast cancer** cell line (21MT) expressing high levels of PPAR.gamma. illustrates a relative resistance to this consequence of receptor activation.

DETD . . . a molecular level, we examined patterns of gene expression in 21PT cells treated for one week with TZDs (FIG. 18a). **Pioglitazone** (Pio) treatment induces mRNA for PPAR.gamma. in these cells, as has been shown in fat differentiation [Brun, R. P. et. . . 10:974-984 (1996)]. lg268 (LG), an RXR specific ligand also does this, but to a more limited extent. The combination of **pioglitazone** and LG268 at these doses is not more effective than the TZD alone. These agents do not lead to expression. . . al. Science 256:526-529 (1994)]. The expression of this mRNA is almost undetectable in vehicle treated cells but is induced by **pioglitazone** treatment. Conversely, keratin 19 (K19) and mucin-1 (Muc-1), two genes whose expression have been used as markers of malignancy [Regimbald, L. H. et al. Cancer Research 56:4244-4249 (1995)], are suppressed by treatment with either **pioglitazone** or LG268. Some markers (Muc-1 and K19) are almost as sensitive to RXR stimulation as they are to the activation. . .

DETD . . . thymidine incorporation in sparse, rapidly growing cultures of 21PT cells. As shown in FIG. 18b, four days of treatment with **pioglitazone** or troglitazone results in a 30% decrease in the incorporation of thymidine. After eight days there was a further increase. . . the vehicle treated cells, reflecting a continuous cell growth. In contrast, in cultures treated with two TZD ligands, troglitazone and **pioglitazone**, there was essentially no further increase in thymidine incorporation, presumably due to a decreased growth rate in these cells. It. . .

DETD The activation of PPAR.gamma. by TZDs causes a remarkable morphological and biochemical response in **breast cancer** cells. Neutral lipid accumulation is prominent, as are changes in gene expression. This includes increased expression of a marker of. . .

DETD Activation of PPAR.gamma. causes a slowing or cessation of cell growth in the **breast cancer** cells studied here. This is not a sudden, cytotoxic response, but appears to be more a differentiative response, occurring over. . . and this modification results in a dramatic reduction in transcriptional and adipogenic activity of this receptor. Since many cancers, including **breast cancer** have been associated with elevated levels and/or activity of MAP kinase [Sivamaran, V. S. et al., Journal Clinical Investigation 99:1478-1483. . .

CLM What is claimed is:

6. The method of claim 5, wherein the PPAR.gamma. agonist is a compound selected from the group consisting of **pioglitazone**, troglitazone, ciglitazone, englitazone, and BRL49653.

. . . myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, **breast cancer**, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary. . .

29. The pharmaceutical composition of claim 28, wherein the PPAR.gamma. agonist is a compound selected from the group of **pioglitazone**, troglitazone, ciglitazone, englitazone, and BRL49653.

L2 ANSWER 2 OF 4 USPATFULL
AN 2001:25934 USPATFULL
TI Human leukocyte 12-lipoxygenase and its role in the pathogenesis of disease states
IN Nadler, Jerry L., La Crescenta, CA, United States
Natarajan, Rama, Hacienda Heights, CA, United States
PA City of Hope, Duarte, CA, United States (U.S. corporation)
PI US 6191169 B1 20010220
WO 9634943 19961107 <--
AI US 1997-945744 19971103 (8)
WO 1996-US6328 19960503
19971103 PCT 371 date
19971103 PCT 102(e) date
RLI Continuation-in-part of Ser. No. US 1995-434681, filed on 4 May 1995, now abandoned Continuation-in-part of Ser. No. WO 1994-US89, filed on 4 Jan 1994 Continuation-in-part of Ser. No. US 1992-936660, filed on 28 Aug 1992, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Criares, Theodore J.
LREP Rothwell, Figg, Ernst & Manbeck
CLMN Number of Claims: 15
ECL Exemplary Claim: 1
DRWN 38 Drawing Figure(s); 24 Drawing Page(s)
LN.CNT 1665
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to a method for inhibiting the etiology of disease in patients having a disease state caused by an excess of 12-lipoxygenase or its products. In particular, the invention provides for administration of a human leukocyte 12-lipoxygenase pathway inhibitor to inhibit disease etiology, to inhibit the proliferation of **breast cancer** and to increase insulin receptor phosphorylation in a patient having Type II diabetics.
PI US 6191169 B1 20010220
WO 9634943 19961107 <--
AB . . . invention provides for administration of a human leukocyte 12-lipoxygenase pathway inhibitor to inhibit disease etiology, to inhibit the proliferation of **breast cancer** and to increase insulin receptor phosphorylation in a patient having Type II diabetics.
SUMM . . . of 12-LO enzyme (hl 12-LO) and its role in the pathogenesis of several major disease states or processes, including atherosclerosis, **breast cancer**, autoimmune and inflammatory disease, diabetic vascular and kidney disease and insulin resistance. There are several features of this unique enzyme. . .
SUMM . . . leucocyte type 12-LO in human monocytes, aortic vascular smooth muscle and endothelial cells, cardiac myocytes, skeletal muscle, the kidney and **breast cancer** cells and beta cells of pancreatic islets. These sites of activity of this enzyme allow a tissue specific role in. . .
DETD Role of the 12-LO Pathway in **Breast Cancer** Cell Growth
DETD Example V of application PCT/US94/00089 indicates that blockage of the 12-LO pathway provides useful human **breast cancer** therapy. A further evaluation of the regulation of 12-LO activity and expression in **breast cancer** cells and tissues confirms that proliferation of **breast cancer** tissue is inhibited by 12-LO inhibitors. Specifically, leukocyte-type 12-LO mRNA expression was studied by a specific reverse transcriptase PCR

method. . . the internal control for PCR, GADPH mRNA 284 bp). 12-LO mRNA levels were also 7- and 11-fold greater in two **breast cancer** cell lines, MCF-7 and COH-BR1 compared to the normal breast epithelial cell line, MCF-10F. In addition, the proliferation of MCF-7. . . mRNA at 24 hours. Hence, activation of the 12-LO pathway appears to play a key role in basal and EGF-induced **breast cancer** cell growth and development.

DETD Role of the 12-LO Pathway in the Action of Estrogen in **Breast Cancer**

DETD It has now been discovered that estrogen, which has been linked to **breast cancer** cell growth and development, plays a role in activating the 12-LO pathway in **breast cancer** cells.

DETD Treatment of cells from the estrogen receptor positive **breast cancer** cell line, MCF-7, with 17.beta.-estradiol for 4 hours in a defined serum-free and phenol red-free medium led to a dose-dependent. . . activity and expression in MCF-7 cells. Hence, activation of the 12-LO pathway appears to play a key role in estrogen-induced **breast cancer** cell growth and development.

DETD Consistent with this data, one aspect of this invention entails therapy to reduce **breast cancer** cell growth and development through inhibition of the 12-LO pathway. Such 12-LO pathway inhibition would, inter alia, reduce the effect estrogen has on **breast cancer** cell growth and development.

DETD . . . the dose-dependent effect of platelet-derived growth factor (PDGF) on vascular endothelial growth factor (VEGF) protein (42 kD) expression in MCF-7 **breast cancer** cells. Nearly confluent MCF-7 cells were serum starved for 24 hours by placing in DME medium+0.4% FCS and 0.2% BSA.. . . a chemiluminiscent technique. It is clearly seen that PDGF causes a dose-dependent increase in the expression of VEGF in the **breast cancer** cells.

DETD . . . illustrates the effect of epidermal growth factor (EGF) and the 12-lipoxygenase product 12-HETE on VEGF protein expression in the MCF-7 **breast cancer** cell line MCF-7. MCF-7 cells were treated with EGF and 12-HETE for 24 hours and VEGF protein identified as described. . .

DETD FIGS. 8 and 9 report data in two human **breast cancer** cell lines MCF-7 and MDA MB that show that the 12-LO product 12-HETE at 10.sup.-7 M and 10.sup.-8 M increases. . .

CLM What is claimed is:

. . . inhibit the expression or activity of said hl 12-lipoxygenase; provided that said hl 12-lipoxygenase pathway inhibitor is not aminoguanidine or **pioglitazone**.

2. The method of claim 1, wherein said disease state is Type II diabetes or **breast cancer**.

5. A method for inhibiting the proliferation of **breast cancer** tissue in a human patient which comprises administering to said patient a therapeutically effective amount of a drug which inhibits hl 12-lipoxygenase expression or activation; provided that said hl 12-lipoxygenase inhibitor is not aminoguanidine or **pioglitazone**.

7. The method of claim 5, in which the proliferation of **breast cancer** tissue is basal, epidermal growth factor-induced or estrogen-induced.

8. A method for mediating **breast cancer** cell growth and development which comprises administering to a patient in need

thereof a therapeutically effective amount of a hl 12-lipoxygenase pathway inhibitor; provided that said hl 12-lipoxygenase pathway inhibitor is not aminoguanidine or **pioglitazone**.

10. The method of claim 8 in which the **breast cancer** cell growth and development is basal, epidermal growth factor-induced or estrogen-induced.

. . . pathway inhibitor which decreases mitogenic activity in said patient; provided that said hl 12-lipoxygenase pathway inhibitor is not aminoguanidine or **pioglitazone**.

14. The method of claim 11, wherein the disease state is Type II diabetes or **breast cancer**.

15. A method for increasing insulin receptor phosphorylation in a patient having Type II diabetes which comprises administering to the. . . hl 12-lipoxygenase pathway products from inhibiting insulin receptor phosphorylation; provided that said hl 12-lipoxygenase pathway inhibitor is not aminoguanidine or **pioglitazone**.

L2 ANSWER 3 OF 4 USPATFULL
AN 1998:119160 USPATFULL
TI Use of troglitazone and related compounds for the treatment of the climacteric symptoms
IN Urban, Randall J., Friendswood, TX, United States
Green, Allan, Galveston, TX, United States
PA Board of Regents, The University of Texas System, Austin, TX, United States (U.S. corporation)
PI US 5814647 19980929 <--
AI US 1997-811419 19970304 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Goldberg, Jerome D.
LREP Arnold White & Durkee
CLMN Number of Claims: 24
ECL Exemplary Claim: 1
DRWN 14 Drawing Figure(s); 14 Drawing Page(s)
LN.CNT 1525
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention is directed toward the use of the drug Troglitazone and related thiazolidinedione compounds in the treatment of the climacteric and cancer. This use is based on the novel discovery that Troglitazone inhibits steroidogenesis in granulosa cell cultures. This activity is believed to result from the ability of thiazolidinedione derivatives to act as a ligand for the orphan steroid receptor peroxisome proliferator-activated receptor gamma (PPAR.gamma.). Troglitazone and related compounds can therefore be used to prevent excessive uterine bleeding during. Further, enhanced translocation of this orphan nuclear receptor into the nucleus of cells will block transcription in rapidly proliferating cancer cells that express PPAR.gamma., resulting in loss of cell viability.
PI US 5814647 19980929 <--
SUMM . . . treatments have many associated risks and side effects. Risks associated with hormone treatment include endometrial carcinoma, hypertension, hyperlipidemia, cholelithiasis (gallstones), **breast cancer**, and deep venous thrombosis (Barentsen, 1996).
SUMM . . . herein referred to as thiazolidine derivatives. Where

appropriate, the specific names of thiazolidine derivatives may be used including: Troglitazone, cioglitazone, **pioglitazone** and BRL 49653.

DRWD . . . treated with Troglitazone and related thiazolidinedione compounds. Porcine granulosa cells were treated for 24 h with increasing doses of Troglitazone, **pioglitazone**, and BRL 49653. The data represent the mean.+-.SEM from 3 studies done in triplicate. Progesterone concentrations were corrected for DNA. . .

DRWD . . . treated for 24 h as such: B, control cells; T, Troglitazone 5 .mu.g/ml; BR, BRL 49635 5 .mu.g/ml; and P, **pioglitazone** 5 .mu.g/ml. The nuclear extract was mixed with radioactively-labeled consensus PPRE as described in FIG. 6. FIG. 7B is a. . .

DETD 5-[4-[2-(5-ethylpyridin-2-yl)ethoxyl]benzyl]thiadiazolidine-2,4-dione: (**pioglitazone**);

DETD . . . the study. After granulosa cell attachment, medium containing the FCS was discarded and serum-free medium with varying concentrations of Troglitazone, **pioglitazone** and BRL 49653 was added for 24 h. One ml of medium was collected for measurement of progesterone by an. . .

DETD . . . electrophoretic mobility gel shift assay (EMSA) with 15 .mu.g of nuclear extract protein from porcine granulosa cells treated with Troglitazone, **pioglitazone** and BRL 49653. All three of the compounds, Troglitazone, **pioglitazone** and BRL 49653 increased binding to the PPRE in granulosa cell nuclear extracts (FIG. 6), indicating that all three compounds. . .

DETD . . . of PPAR.gamma. to the DR-1 consensus sequence after treatment with Troglitazone, cultures of porcine granulosa cells were treated with Troglitazone, **pioglitazone**, and BRL 49653 (all at a 5 .mu.g/ml concentration) and nuclear extract protein was collected. As shown in FIG. 7A. . .

DETD A non-PPAR.gamma. expressing human **breast cancer** cell line, MCF-7, was tested. In this cell line, which is non-mesenchymal in origin, cell viability decreased only with high. . .

DETD . . . of prolonged bleeding. In the case of a patient with a history of deep venous thrombosis, severe hypertension, severe hyperlipidemia, **breast cancer**, endometrial cancer, or cholelithiasis, Troglitazone would be the primary treatment option. In the absence of these risk factors, Troglitazone may. . .

CLM What is claimed is:

12. The method of claim 9 wherein the compound is **pioglitazone**.

24. A method of treating a climacteric symptoms in a climacteric woman patient comprising administering said patient a therapeutically effective. . . group consisting of: (+)-5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl) methoxy]phenyl]methyl]-2,4-thiazolidinedione: (troglitazone); 4-(2-naphthylmethyl)-1,2,3,5-oxathiadiazole-2-oxide; 5-[4-[2-[N-(benzoxazol-2-yl)-N-methylamino]ethoxy]benzyl]-5-methylthiazolidine -2,4-dione; 5-[4-[2-[2,4-dioxo-5-phenylthiazolidin-3-yl)ethoxy]benzyl]thiazolidine-2,4-dione; 5-[4-[2-[N-methyl-N-(phenoxycarbonyl)amino]ethoxy]benzyl]thiazolidine-2,4-dione; 5-[4-(2-phenoxyethoxy)benzyl]thiazolidine-2,4-dione; 5-[4-[2-(4-chlorophenyl)ethylsulfonyl]benzyl]thiazolidine-2,4-dione; 5-[4-[3-(5-methyl-2-phenyloxazol-4-yl)propionyl]benzyl]thiazolidine-2,4-dione; 5-[4-[(1-methylcyclohexyl)methoxy]benzyl]thiadiazolidine-2,4-dione: (ciglitazone); 5-[[4-(3-hydroxy-1-methylcyclohexyl)methoxy]benzyl]thiadiazolidine-2,4-dione; 5-[4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxyl]benzyl]thiadizolidione-2,4-dione; 5-[4-[2-(5-ethylpyridin-2-yl)ethoxyl]benzyl]thiadiazolidine-2,4-dione: (**pioglitazone**);

INCL INCLM: 514/301.000
INCLS: 514/229.800; 514/302.000; 540/476.000; 540/593.000; 546/114.000; 546/115.000; 546/116.000; 548/453.000
NCL NCLM: 514/301.000
NCLS: 514/229.800; 514/302.000; 540/476.000; 540/593.000; 546/114.000; 546/115.000; 546/116.000; 548/453.000
IC [7]
ICM: A61K031-435
ICS: C07D471-04
EXF 546/114; 546/115; 546/116; 514/301; 514/302
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 3 OF 14 USPATFULL
AN 2002:149160 USPATFULL
TI Sulfide and disulfide compounds and compositions for cholesterol management and related uses
IN Dasseux, Jean-Louis Henri, Brighton, MI, UNITED STATES
Oniciu, Carmen Daniela, Ann Arbor, MI, UNITED STATES
PI US 2002077316 A1 20020620
AI US 2001-976898 A1 20011011 (9)
PRAI US 2000-239231P 20001011 (60)
DT Utility
FS APPLICATION
LN.CNT 5040
INCL INCLM: 514/090.000
INCLS: 514/095.000; 514/301.000; 514/378.000; 514/382.000; 514/390.000; 514/432.000; 514/438.000; 549/005.000; 549/006.000; 549/014.000; 549/059.000; 549/060.000; 548/313.100; 548/252.000; 548/247.000; 548/112.000; 546/114.000
NCL NCLM: 514/090.000
NCLS: 514/095.000; 514/301.000; 514/378.000; 514/382.000; 514/390.000; 514/432.000; 514/438.000; 549/005.000; 549/006.000; 549/014.000; 549/059.000; 549/060.000; 548/313.100; 548/252.000; 548/247.000; 548/112.000; 546/114.000
IC [7]
ICM: C07D049-14
ICS: C07D413-14; A61K031-675; A61K031-4743; A61K031-4178; A61K031-42; A61K031-382; A61K031-381
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 4 OF 14 USPATFULL
AN 2002:75470 USPATFULL
TI Dithiolane derivatives
IN Pershadsingh, Harrihar A., Bakersfield, CA, United States
Avery, Mitchell A., Oxford, MS, United States
PA Bethesda Pharmaceuticals, Inc., Bakersfield, CA, United States (U.S. corporation)
PI US 6369098 B1 20020409
AI US 2000-684738 20001004 (9)
PRAI US 1999-157890P 19991005 (60)
US 2000-185347P 20000226 (60)
US 2000-225907P 20000817 (60)
DT Utility
FS GRANTED
LN.CNT 3404
INCL INCLM: 514/440.000
INCLS: 549/032.000; 549/035.000; 549/039.000
NCL NCLM: 514/440.000
NCLS: 549/032.000; 549/035.000; 549/039.000
IC [7]

ICM: A61K031-385
ICS: C07D339-02
EXF 514/440; 549/35; 549/39; 549/32
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 5 OF 14 USPATFULL
AN 2002:55055 USPATFULL
TI Substituted stilbenes as glucose uptake enhancers
IN Patterson, John, Mountain View, CA, UNITED STATES
Park, Sophia Jeong-Weon, Emeryville, CA, UNITED STATES
Lum, Robert T., Palo Alto, CA, UNITED STATES
Spevak, Wayne R., Albany, CA, UNITED STATES
PI US 2002032218 A1 20020314
AI US 2001-872763 A1 20010531 (9)
PRAI US 2000-208591P 20000602 (60)
DT Utility
FS APPLICATION
LN.CNT 1544
INCL INCLM: 514/317.000
INCLS: 514/466.000; 514/534.000; 514/617.000; 546/233.000; 549/436.000; 560/041.000; 564/161.000
NCL NCLM: 514/317.000
NCLS: 514/466.000; 514/534.000; 514/617.000; 546/233.000; 549/436.000; 560/041.000; 564/161.000
IC [7]
ICM: A61K031-445
ICS: A61K031-36; A61K031-166; A61K031-24
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 6 OF 14 USPATFULL
AN 2002:32700 USPATFULL
TI Substituted piperidines as melanocortin receptor agonists
IN Palucki, Brenda L., Hillsborough, NJ, UNITED STATES
Barakat, Khaled J., Brooklyn, NY, UNITED STATES
Guo, Liangqin, Edison, NJ, UNITED STATES
Lai, Yingjie, Edison, NJ, UNITED STATES
Nargund, Ravi P., East Brunswik, NJ, UNITED STATES
Park, Min K., Whippany, NJ, UNITED STATES
Pollard, Patrick G., Oakhurst, NJ, UNITED STATES
Sebhat, Iyassu K., Hoboken, NJ, UNITED STATES
Ye, Zhixiong, Princeton, NJ, UNITED STATES
PI US 2002019523 A1 20020214
AI US 2001-812965 A1 20010320 (9)
PRAI US 2000-191442P 20000323 (60)
US 2000-242265P 20001020 (60)
DT Utility
FS APPLICATION
LN.CNT 4285
INCL INCLM: 544/060.000
INCLS: 544/129.000; 544/360.000; 544/349.000
NCL NCLM: 544/060.000
NCLS: 544/129.000; 544/360.000; 544/349.000
IC [7]
ICM: C07D471-02
ICS: C07D417-02; C07D413-02
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 7 OF 14 USPATFULL
AN 2002:12568 USPATFULL
TI METHODS AND PHARMACEUTICAL COMPOSITIONS FOR INHIBITING TUMOR CELL GROWTH

IN SPIEGELMAN, BRUCE M., WABAN, MA, UNITED STATES
ALTIOK, SONER, BOSTON, MA, UNITED STATES
MUELLER, ELISABETTA, BOSTON, MA, UNITED STATES
SARRAF, PASHA, BOSTON, MA, UNITED STATES
TONTONOZ, PETER, SAN DIEGO, CA, UNITED STATES
PA Dana-Farber Cancer Institute (U.S. corporation)
PI US 2002006950 A1 20020117
AI US 1997-923346 A1 19970904 (8)
RLI Continuation of Ser. No. US 1996-766553, filed on 11 Dec 1996, ABANDONED
DT Utility
FS APPLICATION
LN.CNT 2290
INCL INCLM: 514/401.000
NCL NCLM: 514/401.000
IC [7]
ICM: A61K031-415
ICS: A01N043-50
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 8 OF 14 USPATFULL
AN 2001:202646 USPATFULL
TI Ophthalmic uses of PPARgamma agonists and PPARgamma antagonists
IN Pershadsingh, Harrihar A., Bakersfield, CA, United States
Levy, Daniel E., San Carlos, CA, United States
PA Photogenesis, Inc., Los Angeles, CA, United States (U.S. corporation)
PI US 6316465 B1 20011113
AI US 1999-342381 19990628 (9)
PRAI US 1998-90937P 19980627 (60)
DT Utility
FS GRANTED
LN.CNT 1661
INCL INCLM: 514/310.000
INCLS: 514/912.000; 514/914.000
NCL NCLM: 514/310.000
NCLS: 514/912.000; 514/914.000
IC [7]
ICM: A61K031-41
EXF 514/310; 514/912; 514/914
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 9 OF 14 USPATFULL
AN 2001:194440 USPATFULL
TI Method of inhibiting angiogenesis
IN Gerritsen, Mary E., San Mateo, CA, United States
Xin, Xiaohua E., San Francisco, CA, United States
PA Genentech, Inc. (U.S. corporation)
PI US 2001036955 A1 20011101
AI US 2001-865859 A1 20010525 (9)
RLI Continuation of Ser. No. US 1999-443010, filed on 17 Nov 1999, ABANDONED
PRAI US 1999-116530P 19990120 (60)
US 1998-109328P 19981120 (60)
DT Utility
FS APPLICATION
LN.CNT 2090
INCL INCLM: 514/369.000
NCL NCLM: 514/369.000
IC [7]
ICM: A61K031-426
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 10 OF 14 USPATFULL
AN 2001:158319 USPATFULL
TI Treating cancers associated with overexpression of class I family of receptor tyrosine kinases
IN Dannenberg, Andrew J., 7 Gracie Sq., Apt. 14A, New York, NY, United States 10028
Subbaramaiah, Kotha, 43-23 Colden St., Apt. 17K, Flushing, NY, United States 11355
PI US 6291496 B1 20010918
AI US 1999-472179 19991227 (9)
DT Utility
FS GRANTED
LN.CNT 796
INCL INCLM: 514/376.000
INCLS: 435/007.230; 424/130.100; 424/138.100; 424/143.100; 424/155.100; 424/156.100; 548/220.000
NCL NCLM: 514/376.000
NCLS: 424/130.100; 424/138.100; 424/143.100; 424/155.100; 424/156.100; 435/007.230; 548/220.000
IC [7]
ICM: A01N043-76
ICS: A61K031-42; A61K039-395; G01N033-574; C07D263-62
EXF 424/130.1; 424/138.1; 424/143.1; 424/156.1; 424/155.1; 514/376; 548/270; 435/7.23
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 11 OF 14 USPATFULL
AN 2001:97948 USPATFULL
TI Oxyiminoalkanoic acid derivatives with hypoglycemic and hypolipidemic activity
IN Momose, Yu, Takarazuka, Japan
Odaka, Hiroyuki, Kobe, Japan
Imoto, Hiroshi, Kusatsu, Japan
Kimura, Hiroyuki, Sakai, Japan
Sakamoto, Junichi, Toyonaka, Japan
PA Takeda Chemical Industries, Ltd., Osaka, Japan (non-U.S. corporation)
PI US 6251926 B1 20010626
WO 9958510 19991118
AI US 1999-423854 19991115 (9)
WO 1999-JP2407 19990510
19991115 PCT 371 date
19991115 PCT 102(e) date
PRAI JP 1998-127921 19980511
JP 1998-127922 19980511
DT Utility
FS GRANTED
LN.CNT 5841
INCL INCLM: 514/364.000
INCLS: 514/365.000; 514/372.000; 514/374.000; 514/378.000; 548/131.000; 548/143.000; 548/204.000; 548/214.000; 548/235.000; 548/236.000; 548/247.000; 548/248.000
NCL NCLM: 514/364.000
NCLS: 514/365.000; 514/372.000; 514/374.000; 514/378.000; 548/131.000; 548/143.000; 548/204.000; 548/214.000; 548/235.000; 548/236.000; 548/247.000; 548/248.000
IC [7]
ICM: A61K031-4245
ICS: A61K031-421; C07D003-06; A61P029-00
EXF 514/364; 514/365; 514/372; 514/374; 514/378; 548/131; 548/143; 548/204; 548/214; 548/235; 548/236; 548/247; 548/248

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 12 OF 14 USPATFULL
AN 2001:82522 USPATFULL
TI Methods and pharmaceutical compositions for inhibiting tumor cell growth
IN Spiegelman, Bruce M., Waban, MA, United States
Altiok, Soner, Cambridge, MA, United States
Mueller, Elisabetta, Boston, MA, United States
Sarraf, Pasha, Boston, MA, United States
Tontonoz, Peter, San Diego, CA, United States
PA Dana-Farber Cancer Institute, Boston, MA, United States (U.S. corporation)
PI US 6242196 B1 20010605
WO 9825598 19980618
AI US 1999-319769 19990917 (9)
WO 1997-US22879 19971211
19990917 PCT 371 date
19990917 PCT 102(e) date
DT Utility
FS Granted
LN.CNT 2761
INCL INCLM: 435/007.100
INCLS: 435/004.000; 435/018.000; 548/146.000
NCL NCLM: 435/007.100
NCLS: 435/004.000; 435/018.000; 548/146.000
IC [7]
ICM: C12Q001-34
ICS: C12Q001-00; G01N033-53
EXF 435/7.1; 435/4; 435/18; 548/146
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 13 OF 14 USPATFULL
AN 2001:44248 USPATFULL
TI Troglitazone compounds for treating climacteric and **cancer**
IN Urban, Randall J., Friendswood, TX, United States
Green, Allan, Cooperstown, NY, United States
PA Board of Regents, The University Texas System, Austin, TX, United States (U.S. corporation)
PI US 6207690 B1 20010327
AI US 1999-389828 19990903 (9)
RLI Continuation of Ser. No. WO 1998-US4061, filed on 3 Mar 1998
Continuation-in-part of Ser. No. US 1997-811419, filed on 4 Mar 1997, now patented, Pat. No. US 5814674, issued on 29 Sep 1998
DT Utility
FS Granted
LN.CNT 1543
INCL INCLM: 514/369.000
INCLS: 514/252.000; 514/256.000; 514/342.000; 514/360.000; 514/375.000; 514/376.000
NCL NCLM: 514/369.000
NCLS: 514/252.050; 514/254.020; 514/256.000; 514/342.000; 514/360.000; 514/375.000; 514/376.000
IC [7]
ICM: A61K031-44
EXF 514/369; 514/252; 514/256; 514/342; 514/360; 514/375; 514/376
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 14 OF 14 USPATFULL
AN 1998:119160 USPATFULL
TI Use of troglitazone and related compounds for the treatment of the

climacteric symptoms
IN Urban, Randall J., Friendswood, TX, United States
Green, Allan, Galveston, TX, United States
PA Board of Regents, The University of Texas System, Austin, TX, United States (U.S. corporation)
PI US 5814647 19980929
AI US 1997-811419 19970304 (8)
DT Utility
FS Granted
LN.CNT 1525
INCL INCLM: 514/369.000
INCLS: 514/252.000; 514/256.000; 514/342.000; 514/360.000; 514/375.000; 514/376.000
NCL NCLM: 514/369.000
NCLS: 514/252.050; 514/255.050; 514/256.000; 514/342.000; 514/360.000; 514/375.000; 514/376.000
IC [6]
ICM: A61K031-44
ICS: A61K031-425; A61K031-41
EXF 514/252; 514/256; 514/342; 514/360; 514/369; 514/375; 514/376
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=>

nt evidence which suggests that overexpression of PTP1B is statistically correlated with increased levels of p185.sup.c-erb B2 in ovarian and **breast cancer**. The role of PTP1B in the etiology and progression of the disease has not yet been elucidated. Inhibitors of PTP1B may therefore help clarify the role of PTP1B in **cancer** and in some cases provide therapeutic treatment for certain forms of **cancer**.

SUMM . . . an anti-diabetes treatment. Most importantly, the knock-out mice grew normally and were fertile and have exhibited no increased incidence of **cancer**, as obviously there could have been concerns when one considers the mitogenic properties of insulin. From the diabetes perspective, the. . . appear to be insulin action in liver and muscle. This is in contrast to the main target tissue for the **PPAR**.gamma. agonist class of insulin sensitizers (the "-diones"), which is adipose tissue (Murphy & Nolan, Exp. Opin. Invest. Drugs 9: 1347-1361. . . resistance to weight gain when placed on a high-fat diet. This is again in contrast to the action of the **PPAR**.gamma. agonist class of insulin sensitizers, which rather induce weight gain (Murphy & Nolan, supra), and would suggest that inhibition of. . .

SUMM Further, PTPases influences the following hormones or diseases or disease states: somatostatin, the immune system/autoimmunity, cell-cell interactions/**cancer**, platelet aggregation, osteoporosis, and microorganisms, as disclosed in PCT Publication WO 99/15529.

SUMM . . . are due to a direct effect on the target cells. As an example, somatostatin analogs inhibit the growth of pancreatic **cancer** presumably via stimulation of a single PTPase, or a subset of PTPases, rather than a general activation of PTPase levels. . .

SUMM PTPases: Cell-cell Interactions/**cancer**

SUMM . . . transformation by the oncogenic form of the HER2/neu gene was suppressed in NIH 3T3 fribroblasts overexpressing PTP1B (Brown-Shimer et al., **Cancer** Res. 52: 478-482 (1992)).

SUMM . . . expression level of PTP1B was found to be increased in a mammary cell line transformed with neu (Zhay et al., **Cancer** Res. 53: 2272-2278 (1993)). The intimate relationship between tyrosine kinases and PTPases in the development of **cancer** is further evidenced by the finding that PTP.epsilon. is highly expressed in murine mammary tumors in transgenic mice over-expressing c-neu. . .

SUMM . . . transformation of rat embryo fibroblasts (Zheng, supra). In addition, SAP-1 was found to be highly expressed in pancreatic and colorectal **cancer** cells. SAP-1 is mapped to chromosome 19 region q13.4 and might be related to carcinoembryonic antigen mapped to 19q13.2 (Uchida. . . Inhibitors of specific PTPases are therefore likely to be of significant therapeutic value in the treatment of certain forms of **cancer**.

SUMM . . . hormone) agonists, UCP 2 or 3 (uncoupling protein 2 or 3) modulators, leptin agonists, DA agonists (bromocriptin, doprexin), lipase/amylase inhibitors, **PPAR** (peroxisome proliferator activated receptor) modulators, RXR (retinoid X receptor) modulators or TR .beta. agonists.

SUMM . . . modifying the lipid metabolism such as antihyperlipidemic agents and antilipidemic agents as HMG CoA inhibitors (statins), compounds lowering food intake, **PPAR** and RXR agonists and agents acting on the ATP-dependent potassium channel of the .beta.-cells.

SUMM In still another embodiment the present compounds are administered in combination with a thiazolidinedione e.g. troglitazone, ciglitazone, **pioglitazone**, rosiglitazone or compounds disclosed in WO 97/41097 such as 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione or a

pharmaceutically acceptable salt thereof, preferably the potassium salt.

CLM What is claimed:

. . . method of treating immune dysfunctions including autoimmunity, diseases with dysfunctions of the coagulation system, allergic diseases, osteoporosis, proliferative disorders including **cancer** and psoriasis, diseases with decreased or increased synthesis or effects of growth hormone, diseases with decreased or increased synthesis of. . . 74. The method according to claim 73, wherein the thiazolidinedione is seleceted from troglitazone, ciglitazone, **pioglitazone**, rosiglitazone, and 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione or a pharmaceutically acceptable salt thereof.

L4 ANSWER 3 OF 14 USPATFULL

AN 2002:149160 USPATFULL

TI Sulfide and disulfide compounds and compositions for cholesterol management and related uses

IN Dasseux, Jean-Louis Henri, Brighton, MI, UNITED STATES
Oniciu, Carmen Daniela, Ann Arbor, MI, UNITED STATES

PI US 2002077316 A1 20020620

AI US 2001-976898 A1 20011011 (9)

PRAI US 2000-239231P 20001011 (60)

DT Utility

FS APPLICATION

LREP PENNIE AND EDMONDS, 1155 AVENUE OF THE AMERICAS, NEW YORK, NY, 100362711

CLMN Number of Claims: 42

ECL Exemplary Claim: 1

DRWN 5 Drawing Page(s)

LN.CNT 5040

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to novel sulfide and disulfide compounds, compositions comprising sulfide and disulfide compounds, and methods useful for treating and preventing cardiovascular diseases, dyslipidemias, dysproteinemias, and glucose metabolism disorders comprising administering a composition comprising an ether compound. The compounds, compositions, and methods of the invention are also useful for treating and preventing Alzheimer's Disease, Syndrome X, peroxisome proliferator activated receptor-related disorders, septicemia, thrombotic disorders, obesity, pancreatitis, hypertension, renal disease, **cancer**, inflammation, and impotence. In certain embodiments, the compounds, compositions, and methods of the invention are useful in combination therapy with other therapeutics, such as hypocholesterolemic and hypoglycemic agents.

AB . . . treating and preventing Alzheimer's Disease, Syndrome X, peroxisome proliferator activated receptor-related disorders, septicemia, thrombotic disorders, obesity, pancreatitis, hypertension, renal disease, **cancer**, inflammation, and impotence. In certain embodiments, the compounds, compositions, and methods of the invention are useful in combination therapy with. . .

SUMM . . . metabolism; Alzheimer's Disease; Syndrome X; a peroxisome proliferator activated receptor-associated disorder; septicemia; a thrombotic disorder; obesity; pancreatitis; hypertension; renal disease; **cancer**; inflammation; and impotence. The compound of the invention can also treat or prevent inflammatory processes and diseases like gastrointestinal disease,. . .

SUMM . . . and Fujiki, 1985, Ann. Rev. Cell Biol. 1:489-530; Vamecq and Draye, 1989, Essays Biochem. 24:1115-225; and Nelali et al., 1988, **Cancer** Res. 48:5316-5324). Chemicals included in this group are the fibrate class of hypolipidermic drugs, herbicides, and phthalate

plasticizers (Reddy and. . .

SUMM . . . receptor superfamily activated by these chemicals (Isseman and Green, 1990, Nature 347:645-650). This receptor, termed peroxisome proliferator activated receptor .alpha. (**PPAR**.sub..alpha.), was subsequently shown to be activated by a variety of medium and long-chain fatty acids. **PPAR**.sub..alpha. activates transcription by binding to DNA sequence elements, termed peroxisome proliferator response elements (PPRE), in the form of a heterodimer. . . Sci. USA 90:2160-2164; Heyman et al., 1992, Cell 68:397-406, and Levin et al., 1992, Nature 355:359-361). Since the discovery of **PPAR**.sub..alpha., additional isoforms of **PPAR** have been identified, e.g., **PPAR**.sub..beta., **PPAR** .sub..gamma. and **PPAR**.sub..delta., which have similar functions and are similarly regulated.

SUMM . . . in Keller and Whali, 1993, TEM, 4:291-296; see also Staels and Auwerx, 1998, Atherosclerosis 137 Suppl:S19-23). The nature of the **PPAR** target genes coupled with the activation of PPARs by fatty acids and hypolipidemic drugs suggests a physiological role for the. . .

SUMM . . . useful in medical applications for treating or preventing cardiovascular diseases, dyslipidemias, dyslipoproteinemias, disorders of glucose metabolism, Alzheimer's Disease, Syndrome X, **PPAR** -associated disorders, septicemia, thrombotic disorders, obesity, pancreatitis, hypertension, renal diseases, **cancer**, inflammation, and impotence. As used herein, the phrase "compounds of the invention" means, collectively, the compounds of formulas I, II,. . .

DETD . . . useful for treating or preventing a cardiovascular disease, dyslipidemia, dyslipoproteinemia, a disorder of glucose metabolism, Alzheimer's Disease, Syndrome X, a **PPAR**-associated disorder, septicemia, a thrombotic disorder, obesity, pancreatitis, hypertension, a renal disease, **cancer**, inflammation, and impotence.

DETD . . . present invention provides methods for treating or preventing cardiovascular diseases, dyslipidemias, dyslipoproteinemias, disorders of glucose metabolism, Alzheimer's Disease, Syndrome X, **PPAR** -associated disorders, septicemia, thrombotic disorders, obesity, pancreatitis, hypertension, renal diseases, **cancer**, inflammation, or impotence, comprising administering to a patient in need thereof a therapeutically effective amount of a compound or composition. . .

DETD [0188] **PPAR**: Peroxisome proliferator activated receptor

DETD . . . or at risk of cardiovascular disease, a dyslipidemia, a dyslipoproteinemia, a disorder of glucose metabolism, Alzheimer's Disease, Syndrome X, a **PPAR**-associated disorder, septicemia, a thrombotic disorder, obesity, pancreatitis, hypertension, a renal disease, **cancer**, inflammation, or impotence. In one embodiment, "treatment" or "treating" refers to an amelioration of a disease or disorder, or at. . .

DETD . . . genetic predisposition to a cardiovascular disease, a dyslipidemia, a dyslipoproteinemia, a disorder of glucose metabolism, Alzheimer's Disease, Syndrome X, a **PPAR**-associated disorder, septicemia, a thrombotic disorder, obesity, pancreatitis, hypertension, a renal disease, **cancer**, inflammation, or impotence. Examples of such genetic predispositions include but are not limited to the .epsilon.4 allele of apolipoprotein E,. . .

DETD . . . non-genetic predisposition to a cardiovascular disease, a dyslipidemia, a dyslipoproteinemia, a disorder of glucose metabolism, Alzheimer's Disease, Syndrome X, a **PPAR**-associated disorder, septicemia, a thrombotic disorder, obesity, pancreatitis, hypertension, a renal disease, **cancer**, inflammation, or impotence. Examples

of such non-genetic predispositions include but are not limited to cardiac bypass surgery and percutaneous transluminal. . .

DETD . . . or treating include but are not limited to impaired glucose tolerance; insulin resistance; insulin resistance related breast, colon or prostate **cancer**; diabetes, including but not limited to non-insulin dependent diabetes mellitus (NIDDM), insulin dependent diabetes mellitus (IDDM), gestational diabetes mellitus (GDM),. . .

DETD 4.3.5. **PPAR** Associated Disorders for Treatment or Prevention

DETD [0325] The present invention provides methods for the treatment or prevention of a **PPAR**-associated disorder, comprising administering to a patient a therapeutically effective amount of a compound or a composition comprising a compound of the invention and a pharmaceutically acceptable vehicle, excipient, or diluent. As used herein, "treatment or prevention of **PPAR** associated disorders" encompasses treatment or prevention of rheumatoid arthritis; multiple sclerosis; psoriasis; inflammatory bowel diseases; breast; colon or prostate **cancer**; low levels of blood HDL; low levels of blood, lymph and/or cerebrospinal fluid apo E; low blood, lymph and/or cerebrospinal. . .

DETD [0327] The present invention provides methods for the treatment or prevention of **cancer**, comprising administering to a patient a therapeutically effective amount of a compound or a composition comprising a compound of the. . . fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic **cancer**, **breast cancer**, ovarian **cancer**, prostate **cancer**, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical **cancer**, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic. . . the present invention are insulin resistance or Syndrome X related cancers, including but not limited to breast, prostate and colon **cancer**
.

DETD . . . invention are useful for the treatment or prevention of cardiovascular diseases, dyslipidemias, dyslipoproteinemias, glucose metabolism disorders, Alzheimer's Disease, Syndrome X, **PPAR** -associated disorders, septicemia, thrombotic disorders, obesity, pancreatitis, hypertension, renal disease, **cancer**, inflammation, and impotence.

DETD . . . particular a liposome (see Langer, 1990, Science 249:1527-1533; Treat et al., in Liposomes in the Therapy of Infectious Disease and **Cancer**, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353-365 (1989); Lopez-Berestein, ibid., pp. 317-327; see generally ibid.).

DETD [0358] The present compounds and compositions can also be administered together with a **PPAR** agonist, for example a thiazolidinedione or a fibrate. Thiazolidinediones for use in combination with the compounds and compositions of the invention include but are not limited to 5-((4-(2-(methyl-2-pyridinylamino)ethoxy)phenyl)methyl)-2,4-thiazolidinedione, troglitazone, **pioglitazone**, ciglitazone, WAY-120,744, englitazone, AD 5075, darglitazone, and rosiglitazone. Fibrates for use in combination with the compounds and compositions of the. . . in a preferred embodiment of the present invention, when a

composition of the invention is administered in combination with a **PPAR** agonist, the dosage of the **PPAR** agonist is below that which is accompanied by toxic side effects.

DETD 4.9. Combination Therapy for **Cancer** Treatment

DETD . . . be gamma rays or X-rays. For a general overview of radiation therapy, see Hellman, Chapter 12: Principles of Radiation Therapy **Cancer**, in: Principles and Practice of Oncology, DeVita et al., eds., 2.sup.nd. Ed., J. B. Lippencott Company, Philadelphia. Useful chemotherapeutic agents. . .

L4 ANSWER 4 OF 14 USPATFULL

AN 2002:75470 USPATFULL

TI Dithiolane derivatives

IN Pershadsingh, Harrihar A., Bakersfield, CA, United States
Avery, Mitchell A., Oxford, MS, United States

PA Bethesda Pharmaceuticals, Inc., Bakersfield, CA, United States (U.S. corporation)

PI US 6369098 B1 20020409

AI US 2000-684738 20001004 (9)

PRAI US 1999-157890P 19991005 (60)
US 2000-185347P 20000226 (60)
US 2000-225907P 20000817 (60)

DT Utility

FS GRANTED

EXNAM Primary Examiner: Lambkin, Deborah C.

LREP Townsend and Townsend and Crew LLP

CLMN Number of Claims: 42

ECL Exemplary Claim: 1

DRWN 22 Drawing Figure(s); 22 Drawing Page(s)

LN.CNT 3404

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention describes methods for synthesizing novel dithiolane derivatives, ligands with high affinity for the nuclear hormone receptors, peroxisome proliferator-activated receptor-.gamma. (**PPAR**.gamma.) and/or **PPAR**.alpha.. Methods for using these compounds in the treatment of endocrine, skin, cardiovascular, immunological, neurological, neuropsychiatric, neoplastic and chronic viral diseases of various organs, including the eye are described. Methods of treating proliferative and inflammatory diseases, degenerative diseases, and age-related dysregulations, caused by an hereditary (genetic) condition or an environmental insult are also provided. In addition, methods are provided for treating conditions and diseases comprising the step of administering to a human or an animal in need thereof a therapeutic amount of pharmacological compositions comprising a pharmaceutically acceptable carrier, a **PPAR** .alpha. agonist, and a second agent selected from the following: a **PPAR**.gamma. ligand, or an RXR ligand (rexinoid), or a **PPAR**.gamma./RXR ligand, effective to reverse, slow, stop, or prevent the pathological inflammatory or degenerative process.

AB . . . invention describes methods for synthesizing novel dithiolane derivatives, ligands with high affinity for the nuclear hormone receptors, peroxisome proliferator-activated receptor-.gamma. (**PPAR**.gamma.) and/or **PPAR**.alpha.. Methods for using these compounds in the treatment of endocrine, skin, cardiovascular, immunological, neurological, neuropsychiatric, neoplastic and chronic viral diseases. . . a human or an animal in need thereof a therapeutic amount of pharmacological compositions comprising a pharmaceutically acceptable carrier, a **PPAR**.alpha. agonist, and a second agent selected from the following: a **PPAR**.gamma. ligand, or an RXR ligand (rexinoid), or a **PPAR**.gamma./RXR

ligand, effective to reverse, slow, stop, or prevent the pathological inflammatory or degenerative process.

SUMM . . . nuclear receptor superfamily of ligand-activated transcription factors. Three subtypes of PPARs have been cloned from the mouse and human, i.e., **PPAR**.gamma. and **PPAR**.delta.. In humans, **PPAR**.gamma. and **PPAR**.alpha. are differentially expressed in organs and tissues (see, Willson et al. J Med. Chem. 43:527-50 (2000)).

SUMM Nuclear receptors like **PPAR** possess DNA binding domains (DBDs) that recognize specific DNA sequences (called response elements) located in the regulatory regions of their. . .

SUMM . . . metabolism. Thiazolidinediones, which are a class of oral insulin-sensitizing agents that improve glucose utilization without stimulating insulin release, are selective **PPAR** agonists. U.S. Pat. No. 4,287,200, discloses certain thiazolidine derivatives having the ability to lower blood glucose levels. In addition, U.S.. . . were shown to have the ability to decrease the levels of blood lipid peroxides, blood triglycerides and blood cholesterol. A **PPAR** .gamma. antagonist that inhibits adipocyte differentiation has also been synthesized (see, Oberfield, et al., Proc Natl Acad Sci USA 96:6102-6 (1999)).

SUMM However, recent discoveries suggest that the genes regulated by **PPAR** receptors also play a role in other processes. Binding of ligands to PPARs induce changes in the transcriptional activity of. . . and differentiation, apoptosis, and the activities of iNOS, MMPases and TIMPs. These findings suggest that regulation of the action of **PPAR** may have a therapeutic role in treating diseases such as occlusive vascular diseases (e.g. atherosclerosis), hypertension, neovascular diseases (e.g. diabetic. . .

SUMM The precise contribution of each particular **PPAR** subtype to transcriptional activation of particular genes is difficult to predict. DNA response elements for both **PPAR**.alpha. and **PPAR** .gamma. have been found in the promoter regions of a variety of genes, including a number involved in lipid and fatty. . . For example, in fetal rat brown adipocytes, expression of the uncoupling proteins UCP-1, UCP-2 and UCP-3 is controlled via both **PPAR**.alpha. and **PPAR**.gamma. activation. Activation of **PPAR**.gamma. elicited 5- and 3-fold increases in UCP-1 and UCP-3, respectively. In contrast, activation of **PPAR**.alpha. increased UCP-1 ten-fold, but decreased UCP-3. Interestingly, when both **PPAR** and were activated, a synergistic interaction occurred in regulation of UCP-3.

SUMM . . . 273(2):560-4 (2000)). It is not known whether the nuclear receptor coactivators or corepressors identified to date are selective for particular **PPAR** receptors (see, Spiegelman, et al., Diabetes 47:507-514 (1998)). Many coactivators or corepressors have multiple modes of action and hence it. . . et al. Diabetes 47:507-514 (1998)), strongly suggests that the full spectrum of nuclear cofactors that regulate the transcriptional activity of **PPAR**.gamma. and/or **PPAR**.alpha. remains to be defined.

SUMM Due to this lack of understanding of **PPAR**.gamma. and **PPAR**.alpha.-related activity and mechanisms, as well as the differential expression of **PPAR**.gamma. and **PPAR** .alpha. in cells, it is difficult to ascertain the potential effects of concurrent activation of **PPAR** gamma and alpha receptors on both cellular processes relevant to disease. For example, **PPAR** .alpha. or **PPAR**.gamma. may either have similar or disparate effects. It is known that inflammatory activation of human aortic smooth-muscle cells is inhibited by **PPAR**.alpha., but not by **PPAR**.gamma.. Apoptosis in human monocyte-derived macrophages is induced by activation of either **PPAR**.alpha. and **PPAR**

.gamma. (see, Staels et al. Nature 393:790-3 (1998)); Chinetti, et al. J Biol Chem. 273:25573-80 (1998)). However, **PPAR**.gamma. activation by troglitazone or 15-deoxy-.DELTA.-12-14-prostaglandin J2 protects cerebellar granule cells from cytokine-induced apoptotic cell death (see, Heneka, et al. J. . .

SUMM To summarize, **PPAR** subtypes exhibit differential patterns of tissue expression, different actions on different response elements, differential effects on co-activators and co-repressors, and differential regulation of access to the core transcriptional machinery. This complexity of **PPAR** regulation makes it extremely difficult to predict precisely which genes will ultimately be activated (transcribed) or inactivated (suppressed) as a result of activation by a particular combination of an agonist or an antagonist of **PPAR** .gamma. or **PPAR**.alpha.. As a consequence, it is impossible to predict with certainty the way in which a tissue expressing **PPAR** .gamma. and **PPAR**.alpha. may respond to a particular ligand, or whether a particular pathological state will be attenuated, arrested, accentuated or worsened by said ligand. This is especially the case in which a single ligand activates both **PPAR**.gamma. and **PPAR**.alpha. to similar degrees.

SUMM In view of this complex interplay between **PPAR**.gamma. and **PPAR**.alpha., it is desirable to synthesize compounds, which bind both receptors and can take advantage of potential synergistic effects. For example, **PPAR**.gamma. and **PPAR**.alpha. activation has been shown to inhibit proliferation (see, Ellis, et al. Arch Dermatol. 136:609-616 (2000)) and promote differentiation of epidermal. . .

SUMM The syntheses of thiazolidine dithiolane derivatives with affinity for **PPAR**.gamma. have been described in WO 00/53601, published Sep. 14, 2000. Despite the advances of WO 00/53601, what is needed in the art are non-thiazolidinedione (non-TZD) dithiolane derivatives with high affinity for **PPAR**.gamma. that function either as **PPAR** .gamma. agonists, **PPAR**.gamma. antagonists, or mixed **PPAR**.gamma. agonist/antagonists. Methods to synthesize these non-TZD compounds with high affinity for both **PPAR**.gamma. and **PPAR**.delta., antagonists, mixed (partial) agonist/antagonists, or mixed **PPAR**.gamma./**PPAR**.delta. agonists are also needed. The present invention remedies such needs.

SUMM The present invention provides novel dithiolane derivatives which can be used to ameliorate **PPAR**.gamma.-mediated diseases such as inflammatory and proliferative diseases and those that are characterized by inappropriate activation of nuclear transcription factors.

SUMM In another aspect, the present invention relates to a method of treating a **PPAR**.gamma. mediated disease or oxidative stress, comprising administering a therapeutically effective amount of a compound of the present invention or mixtures thereof to an individual suffering from a **PPAR**.gamma.-mediated disease.

DETD . . . that bind the compound present in a sample or a subject. Thus, in the present invention, the EC.sub.50 of a **PPAR**.gamma. modifier is the concentration of the modifier that activates 50% of the **PPAR**.gamma. present in the sample or organism. The term "activate" has its ordinary meaning, i.e., cause to function or act.

DETD The term "peroxisome proliferator activating receptor-gamma" or "**PPAR**.gamma." refers to either the .gamma..sub.1, .gamma..sub.2 or .gamma..sub.3 isotypes or a combination of all isotypes of **PPAR**.gamma.. PPARs are nuclear receptors which naturally bind to fatty acids and which have been implicated in adipocyte differentiation (see, Perlmann. . .

DETD The term "peroxisome proliferator activating receptor-alpha" is also referred to as "**PPAR**.alpha.".

DETD The terms "**cancer**, neoplasm or malignancy" include primary and metastatic disease. So, for example, cervical **cancer** includes the neoplasm at the primary site (cervix) and metastatic cervical **cancer**, regardless of site of metastasis, such as skeleton, brain, etc.

DETD . . . to those reported by Berger et al. (see, Berger, J., et al., J Biol. Chem., 274:6718-6725 (1999)) known to possess **PPAR** -.gamma. activating properties such as L-796449. The synthesis of a specific example is shown in FIG. 20 (structure 131). In FIG.. . .

DETD In certain aspects, compounds of the present invention are activators of **PPAR**.gamma., **PPAR**.alpha. or activators of both **PPAR**.gamma., **PPAR**.alpha.. Using the assay methods of the present invention is possible to distinguish compounds that are **PPAR**.gamma. modulators, PPARa modulators, or compounds which or both **PPAR**.gamma. and **PPAR**.alpha. modulators.

DETD As described hereinbelow, a transient cotransfection assay can be used to screen for **PPAR** activity. In this assay, chimeras are constructed that fuse the ligand binding domains of each **PPAR** subtype to the DNA binding domain of the yeast transcription factor GAL4. Expression plasmids for the GAL4-**PPAR** chimeras are then transfected into cells with a reporter construct. This general assay system identifies compounds of Formulae A, I, II, III, IV, and V which are activators of **PPAR**.gamma. and/or **PPAR**.alpha. (see, Lehmann et al., J Biol. Chem. 270:12953-12956 (1995) and Murakami, K et al., Biochem. Biophys. Res. Commun. 260: 609-613. . .

DETD In another aspect, the present invention relates to a method of treating a **PPAR**.gamma. mediated disease or oxidative stress, comprising administering to a subject a therapeutically effective amount of a compound of the of the Formulae A, I, II, III, IV, V and mixtures thereof, thereby treating said **PPAR**.gamma. mediated disease or oxidative stress.

DETD . . . aspects, the compounds, composition and methods of the present invention can be used to treat diseases involving tissues that express **PPAR**.gamma., **PPAR**.alpha. and **PPAR**.delta., and more particularly, can be used for treating inflammatory, proliferative, degenerative diseases of multiple organs and tissues, and diseases involving. . . these diseases comprise the administration of an effective amount of any natural or synthetic substance that modifies the activity of **PPAR**.gamma. and/or **PPAR**.alpha..

DETD . . . dose of a compound (or pharmaceutically acceptable salts and solvates thereof in acceptable pharmaceutical excipients) that modifies the activity of **PPAR**.gamma.. The terms "modify and modulate" are defined to include its usually accepted meaning and includes treating a human subject prophylactically. . .

DETD . . . a dose of a compound, or a pharmaceutically acceptable salt, ester, solvate or tautomer thereof, a therapeutic amount that activates **PPAR**.gamma. and/or **PPAR**.alpha.. The specific diseases and associated disorders that can be treated with the compounds are listed in Tables I through X.. . .

DETD . . . as gels such as hydrogel. A preferred embodiment of the present invention involves administration of semi-solid or solid implants containing **PPAR**.gamma. agonists.

DETD In certain other aspects, the methods of the present invention include the use of all existing synthetic and naturally occurring **PPAR** .gamma. agonists and those yet to be discovered. Preferred **PPAR** .gamma. agonists useful for the application of methods described herein include the novel compounds described in the following submitted patent applications:. . .

DETD . . . moiety of lipoic acid as the "targetor moiety". Therefore a preferred therapeutic compound is the 1,2-dithiolane-3-pentyl ester

derivative of any **PPAR**.gamma. or **PPAR**.alpha. agonist and is formulated into solutions, suspensions, aerosols and particulate dispersions appropriate for application to the pulmonary system. The therapeutic. . .

DETD Broadly, for a **PPAR** ligand (**PPAR**.alpha., **PPAR**.gamma. or **PPAR**.delta.), the oral dose is determined from the following formula:

DETD EC50 is the concentration (amount) of compound required to activate or bind to 50% of the **PPAR** ligand in the sample or patient and is in mole/L units;

DETD . . . example, troglitazone is a compound encompassed by the methods of this invention. A man with diagnosis of early stage prostate **cancer** in situ has a lean body weight (LBW) of 70 kg. If k1=10; the EC50 for troglitazone=2.4.times.10 -6 mol/L and. . .

DETD Typically, the dosage per day of a thiazolidinedione of this invention will depend on the affinity of the thiazolidinedione for **PPAR** .gamma.. The dosages of compounds with high affinity, e.g., rosiglitazone, will fall between about 0.5 mg to about 100 mg, of. . .

DETD . . . preferred embodiment, the compounds are administered with food. The fats in food provide a lipid micellular phase in which the **PPAR**.gamma. and/or **PPAR**.alpha. modifiers of this invention can solubilize and be more effectively absorbed.

DETD . . . local treatment will vary depending on the compound used. For example, the thiazolidinediones of this invention have different affinity for **PPAR**.alpha. and/or **PPAR**.gamma., e.g., **pioglitazone** has a higher affinity for **PPAR**.gamma. than troglitazone. Typically, the greater the affinity, the more effective the compound, and the lower the dosage that is an effective amount. Therefore, a lower concentration of **pioglitazone** in a unit dosage form comprises an effective amount.

DETD . . . 0.1 mg to about 1000 mg once or twice a day depending on the binding affinity of the compound for **PPAR**.gamma.. For example, the typical oral dose of the thiazolidinediones, rosiglitazone and **pioglitazone**, presently approved for the treatment of type 2 diabetes mellitus, is 4 to 8 mg and 15 mg to 45. . .

DETD . . . can be similar to the dosages and routes and frequency of administration ordinarily recommended for these agents when given without **PPAR**.gamma. activators. Examples of effective retinoids are 9-cis-retinoic acid, 13-cis-retinoic acid, all-trans-retinoic acid (at-RA). Preferred retinoids for this purpose would include. . . vitamin D analogs are 1,25-dihydroxy-vitamin D, calcipotriene, calcipotriol and cholecalciferol. The dosage range and routes and frequency of administration of **PPAR** .gamma.activators required to achieve synergistic effects when given with vitamin D or retinoid derivatives are the same as those described elsewhere. . . retinoid related compounds for synergistic topical therapy would be similar to those ordinarily recommended for these agents when given without **PPAR**.gamma. activators. The dosage range and the modes and frequency required for topical administration of the flavonoid thiazolidine derivatives given in. . .

DETD Synergistic Activation by **PPAR**.gamma. and **PPAR** .alpha. Ligands

DETD In certain aspects, the compounds of the present invention are **PPAR**.gamma., **PPAR**.alpha. or both **PPAR**.gamma. and **PPAR**.alpha. activators. Activation of both **PPAR** .gamma. and **PPAR**.alpha. have effects on metabolic risk factors that lead to chronic systemic inflammation that can result in diabetes, atherosclerosis, congestive heart. . . effect. One aspect of this invention is the treatment of such diseases that involves the simultaneous pharmacological activation of both **PPAR**.gamma.

and **PPAR**.alpha.. Synergy may be achieved either with a ligand that co-activates both isoforms, or therapeutic compositions comprising a **PPAR**.alpha. agonist and a second compound selected from the group of a **PPAR**.gamma. ligand or a RXR ligand or a **PPAR**.gamma./RXR ligand. Because the PPARs heterodimerize with RXR, activation of RXR provides the synergistic effect in slowing, arresting, reversing or preventing. . .

DETD . . . (see, Neve et al. Biochem Pharmacol, 60:1245-1250 (2000) and Ellis et al. Arch Dermatol,136:609-16 (2000), for discussion). Specific activation of **PPAR**.gamma. on the one hand (see, Ellis et al. Arch Dermatol;136:609-16 (2000)), and specific activation of **PPAR**.alpha. on the other (see, Komuves, LG et al. J Invest Dermatol, 115:353-60 (2000)) have been shown to independently stimulate keratinocyte differentiation and inhibit and epidermal proliferation. Similarly, for example, activation of **PPAR**.gamma. inhibits proliferation of VSM cells, and iNOS production and matrix metalloproteinase (MMP) activity in the vessel wall, whereas activation of **PPAR**.alpha. decreases the activity of cell adhesion moles and affects lipoprotein metabolism, resulting in a profound anti-dyslipidemic systemic effect (see, Neve, BP, et al. Biochem Pharmacol, 60:1245-1250 (2000)). Thus pharmacological co-activation of **PPAR**.gamma. and **PPAR**.alpha. provides synergistic therapy in the treatment of atherosclerosis or psoriasis. Moreover, using the assay methods of the present invention is posssible to distinguish **PPAR**.gamma. modulators, **PPAR**.alpha. modulators, or compounds which or both **PPAR**.gamma. and **PPAR**.alpha. modulors.

DETD Via negative regulation of NF-kappaB and AP-1 signaling pathways, **PPAR**.alpha. inhibits expression of inflammatory genes, such as interleukin-6, cyclooxygenase-2, endothelin-1, and the expression of monocyte-recruiting proteins such as vascular cell. . . inhibits the expression of genes encoding iNOS, MMP-9, scavenger receptor A, VCAM-1. Therefore treatment modalities involving the simultaneous activation of **PPAR**.gamma. and **PPAR**.alpha. provides a synergistic therapeutic effect and leads to superior improvement, resolution or prevention of systemic cardiovascular inflammation, including atherosclerosis, vascular. . .

DETD Phenotypic Targeting of **PPAR**.gamma. and **PPAR**.alpha. Activators

DETD In certain instances, both **PPAR**.gamma. and **PPAR** .alpha. activators have been shown, independently, to suppress expression of inflammatory regulators, inhibit proliferation and promote apoptosis of pathological cellular phenotypes.. . . retinitis (neuro-retinal degenerative diseases), in which prevention of apoptosis is the operative mechanism. Therefore, in these disease states, activation of **PPAR**.gamma. and **PPAR**.alpha. by suppressing transcription of inflammatory cytokines, prevents apoptosis of the target cell and promotes survival of the non-pathological cellular phenotype.. . . microglia, resulting in inappropriately activation and production of harmful inflammatory cytokines (see, Zhang, GX et al. Mult Scler, 6:3-13 (2000)). **PPAR**.gamma. activation can inhibit neuronal apoptosis and promote neuronal protection through the upregulation of neuronal apoptosis inhibitory protein (see, Magun R et al. Diabetes, 47:1948-52 (1998)). Indeed, **PPAR**.gamma. activation protects cerebellar granule cells from cytokine-induced apoptotic cell death (Heneka, MT et al. J Neuroimmunol.,100:156-68 (1999)). Moreover, **PPAR**.alpha. has been shown to suppress inflammatory cytokines and nuclear factors in monocyte/macrophages. A similar mechanism involving suppression of inflammatory cytokine production by microglia would prevent oligodendrocyte apoptosis.

Finally, combined **PPAR**.gamma. and **PPAR**.alpha. activation promotes Th1/Th2 differentiation as a final common pathway to inhibit apoptosis of the non-pathological phenotype and promotion of neuronal. . .

DETD In certain embodiments, **PPAR**.gamma. interactions with co-activators and co-repressors tend to be ligand-specific. For example, the natural **PPAR**.gamma. ligand, 15-deoxy-delta-12,14-prostaglandin J2 can induce the receptor-ligand complex to interact with the cofactors: SRC-1, TIF2, AIB-1, p300, TRAP220/DRIP205, whereas, under the same conditions the anti-diabetic thiazolidinedione, troglitazone, a synthetic **PPAR**.gamma. ligand does not. Therefore, ligand binding may alter **PPAR**.gamma. structure in a ligand-type specific way, resulting in distinct **PPAR**.gamma. coactivator interactions (see, Kodera, Y et al. J Biol Chem. Aug. 15, 2000)). By analogy, a similar mechanism would provide ligand-specific control of gene expression in the case of **PPAR**.alpha. activation.

DETD Preferably, the 4-substituted benzodithiolanyl derivatives described in this invention have been designed to bind with high affinity and activate **PPAR**.gamma.. Preferably, the 3-substituted benzodithiolanyl derivatives described in this invention is a modification whereby this compound will bind with high affinity and activate both **PPAR**.gamma. and **PPAR**.alpha. (see, Willson et al. J Med. Chem., 43:527-50 (2000)).

DETD A **PPAR**.alpha. agonist as specified herein is selected from the group consisting of: a n-3 fatty acid (e.g. alpha-linolenic acid), a n-6. . .

DETD Compounds that also apply to the examples given below include rosiglitazone, **pioglitazone**, KRP 297, MCC 555 and JTT-501. Other compounds relevant to the practice of this invention, including **PPAR**.gamma., **PPAR**.alpha. or **PPAR**.gamma. and **PPAR**.alpha. activators are listed in Table 1 in, Willson et al. J Med. Chem. 43:527-50 (2000). The activation constants (ED50s) shown. . .

DETD **Pioglitazone**: 45 mg once daily

DETD Other **PPAR**.gamma. agonists are selected from the group consisting of an alpha-methoxy-beta-phenyl propanoic acid derivative, an N-(2-Benzoylphenyl)-L-tyrosine derivative, a phenylacetic acid derivative or a **PPAR**.gamma. selective cyclopentenone prostaglandin in the A1 or J2 series.

DETD In screening for compounds that modify the activity of **PPAR** .gamma. and/or **PPAR**.alpha. the following cell systems are employed. Human endothelial cells and vascular smooth muscle (VSM) cells which are known to express both **PPAR**.gamma. and **PPAR** .alpha.. Alternatively, isolated human peripheral T lymphocytes from normal healthy donors or a mammalian cell line such as a Jurkat T. . .

DETD The binding of agonist ligands to the receptor results in changes in the expression level of mRNAs encoded by **PPAR** target genes. This process, "transactivation", is determined by cell-based assays which monitor this functional activity. Transactivation assays use cells that. . . conveniently assayed using standard colorimetric or photometric methods. The procedure used to test the compounds of this invention is the **PPAR**-GAL4 transactivation assay, which uses chimeric receptors where the **PPAR** LBD is fused to the DBD of the yeast transcription factor GAL4 and employs a reporter gene containing a GAL4. . . transfection efficiency using the beta-galactosidase activity as an internal standard. Compounds which elicited on average at least 70% activation of **PPAR** versus rosiglitazone (positive control for PPARgamma specific activation) or versus Wy-14643 (positive control for PPARalpha specific activation) were considered full. . .

DETD . . . not pregnant and does not plan to become pregnant during treatment, a compound known to activate PPARgamma, namely, the thiazolidinedione, **pioglitazone** is administered orally in a dosage of 30 milligrams daily. The patient is evaluated by an ophthalmologist experienced in the. . .

DETD . . . of allograft rejection. The identical experiment is conducted on a control animal given placebo in place of the rosiglitazone or **pioglitazone**. Histological evidence of rejection is reduced or prevented by treatment with the rosiglitazone or **pioglitazone**. To monitor the protection from chronic allograft rejection by the test drug, the identical experiment is performed but therapy is. . .

DETD . . . group consisting of: compound 92, 2 mg twice daily; a thiazolidinedione given orally, e.g. rosiglitazone, 4 mg twice daily or **pioglitazone**, 45 mg once daily). Examples of synergistic combinations are as follows:

DETD Treatment of Chronic Recalcitrant Multiple Sclerosis by Oral Administration of **Pioglitazone**--A Clinical Trial

DETD . . . not pregnant and does not plan to become pregnant during treatment, a compound known to activate PPARgamma, namely, the thiazolidinedione, **pioglitazone** is administered orally in a dosage of 15 milligrams daily during the acute episode, and is titrated up to 30. . .

DETD . . . for therapy. The approach is the same as for the foregoing patient, except that the starting dose of 30 mg **pioglitazone** once daily for 3 months, and is increased to 45 mg thereafter. Regression of the disease or improvement in his. . .

DETD Combination Treatment of a **PPAR**-Mediated Inflammatory, Proliferative or Degenrative Disease with PPARalpha Agonist and a PPARgamma Agonist--A Clinical Trial

DETD The **PPAR**-mediated disease is selected from one of the following: a degenerative neurological disease (Alzheimer's disease) or a degenerative retinal disease (a. . .

DETD . . . from: compound 92 (this invention, 1 or 2 mg twice daily oral dose), rosiglitazone (4 mg twice daily oral dose), **pioglitazone** (30 or 45 mg daily oral dose). These pharmacological compositions may be used to treat acute or chronic disease or. . .

DETD . . . inflammatory ischemic vascular disease), ulcerative colitis (an inflammatory bowel disease), hepatic fibrosis (a degenerative liver disease), or breast or prostate **cancer** (a carcinogenic disease). The diagnosis is confirmed by clinical laboratory and pathological diagnostic tests. The patient is evaluated by a. . . not pregnant and does not plan to become pregnant during treatment, a compound known to activate PPARgamma, namely, the thiazolidinedione, **pioglitazone** (Actos, Takeda USA) is administered orally in a dosage of 15 milligrams daily, and is titrated up to 30 mg. . .

DETD Treatment of a **PPAR**-Mediated Inflammatory, Proliferative or Degenerative Disease with Compound which Activates both PPARalpha and PPARgamma--A Clinical Trial

DETD Combination Treatment of a **PPAR**-Mediated Inflammatory, Proliferative or Degenerative Disease with PPARgamma Agonist or a Mixed PPARgamma/PPARalpha Agonist (Co-Ligand) and an Estrogen Receptor Ligand--A Clinical. . .

DETD The **PPAR**-mediated disease is selected from one of the following: a degenerative neurological (Alzheimer's disease) or retinal disease, arthritis, atherosclerosis, depression, diabetes. . .

DETD Combination Treatment of a **PPAR**-Mediated Inflammatory, Proliferative Dermatological (Skin) Disease with PPARgamma Agonist or a Mixed PPARaamma/PPARalpha Agonist (Co-Ligand) and a Vitamin D Receptor Ligand--A. . .

DETD The **PPAR**-mediated disease is an inflammatory, proliferative or

degenerative skin disease such as psoriasis, keratitis, hidradenitis, ichthyosis, acne, rosacea, verrucae and other. . .

DETD . . . specific agonists are selected from the group consisting of: a thiazolidinedione given orally, e.g. rosiglitazone, 4 mg twice daily or **pioglitazone**, 45 mg once daily). Examples of mixed PPARgamma/PPARalpha co-ligands are KRP 297 (50 to 500 mg, daily oral dose). The. . .

DETD

TABLE VIa

Examples of the neoplastic diseases treatable using compounds described in this invention

Organ System Malignancy/**Cancer** type

Skin Basal cell carcinoma, melanoma, squamous cell carcinoma; cutaneous T cell lymphoma; Kaposi's sarcoma.

Hemato-logical. . . Acute leukemia, chronic leukemia and myelodysplastic virus infection.

Neuro-logical Gliomas including glioblastomas, astrocytoma, ependymoma, medulloblastoma, oligodendroma; meningioma, pituitary adenoma, neuroblastoma, craniopharyngioma.

Gastro-intestinal Colon, colorectal, gastric, esophageal, mucocutaneous carcinomas.

Breast **Breast cancer** including estrogen receptor and progesterone receptor positive or negative subtypes, soft tissue tumors.

Metastasis Metastases resulting from all neoplasms.

Other Angiomata, angiogenesis. . .

DETD

TABLE VIa

Examples of the neoplastic diseases treatable using compounds described in this invention

Organ System Malignancy/**Cancer** type

Skin Basal cell carcinoma, melanoma, squamous cell carcinoma; cutaneous T cell lymphoma; Kaposi's sarcoma.

Hemato-logical. . . Acute leukemia, chronic leukemia and myelodysplastic virus infection.

Neuro-logical Gliomas including glioblastomas, astrocytoma, ependymoma, medulloblastoma, oligodendroma; meningioma, pituitary adenoma, neuroblastoma, craniopharyngioma.

Gastro-intestinal Colon, colorectal, gastric, esophageal, mucocutaneous carcinomas.

Breast **Breast cancer** including estrogen receptor and progesterone receptor positive or negative subtypes, soft tissue tumors.

Metastasis Metastases resulting from all neoplasms.

Other Angiomata, angiogenesis. . .

DETD

TABLE VII

Examples of viral infections and related pathologies treatable according to the methods of this invention

Virus Viral infection/**cancer** or other virus-associated pathology

HTLV T-cell leukemia/lymphoma, HTLV-associated arthritides/myelopathies.

HPV Cervical and anogenital cancers; common and anogenital (venereal) warts, including verrucae, condyloma. . .
DETD . . . described in this invention
Organ system Viral infection/manifestation or other HIV-associated disease

Immunologic AIDS, primary HIV infection.
Dermatological Anogenital cancers including rectal and cervical **cancer**, Kaposi's sarcoma, atopic dermatitis, squamous cell carcinoma, hairy leukoplakia, molluscum contagiosum, warts (HPV infections), seborrheic dermatitis, psoriasis, xeroderma, HSV and. . .

CLM What is claimed is:

30. A method of treating a **PPAR**.gamma. or **PPAR**.alpha. mediated disease or oxidative stress, said method comprising administering to a subject a therapeutically effective amount of a compound of. . . S, N, resulting in N--O, N--S, and N--N bonds or a pharmaceutical acceptable salt or solvate thereof, thereby treating said **PPAR**.gamma. or **PPAR**.alpha. mediated disease or oxidative stress.

31. A method of treating a **PPAR**.gamma. or **PPAR**.alpha. mediated disease or oxidative stress according to claim 30, said compound having the formula ##STR31## wherein: R is a member. . . S, N, resulting in N--O, N--S, and N--N bonds, or a pharmaceutical acceptable salt or solvate thereof, thereby treating said **PPAR**.gamma. or **PPAR**.alpha. mediated disease or oxidative stress.

32. A method of treating a **PPAR**.gamma. or **PPAR**.alpha. mediated disease or oxidative stress according to claim 30, said compound having the formula ##STR32## wherein: R is a member. . . S, N, resulting in N--O, N--S, and N--N bonds, or a pharmaceutical acceptable salt or solvate thereof, thereby treating said **PPAR**.gamma. or **PPAR**.alpha. mediated disease or oxidative stress.

33. A method of treating a **PPAR**.gamma. or **PPAR**.alpha. mediated disease or oxidative stress, said method comprising administering to a subject a therapeutically effective amount of a compound of. . . to 4 inclusive; and p is 0 or 1, or a pharmaceutical acceptable salt or solvate thereof, thereby treating said **PPAR**.gamma. or **PPAR**.alpha. mediated disease or oxidative stress.

34. A method of treating a **PPAR**.gamma. or **PPAR**.alpha. mediated disease or oxidative stress according to claim 30, said compound having the formula ##STR34## wherein: R is a member. . . S, N, resulting in N--O, N--S, and N--N bonds, or a pharmaceutical acceptable salt or solvate thereof, thereby treating said **PPAR**.gamma. or **PPAR**.alpha. mediated disease or oxidative stress, acceptable carrier.

35. A method of treating a **PPAR**.gamma. or **PPAR**.alpha. mediated disease or oxidative stress according to claim 30, said compound having the formula: ##STR35## wherein: R.sup.5 and R.sup.6 are. . . is 0 or 1, or a pharmaceutical acceptable salt or solvate thereof; and a pharmaceutical acceptable carrier, thereby treating said **PPAR**.gamma. or **PPAR**.alpha. mediated disease or oxidative stress.

. . . degenerative disease of mammalian tissues, said method comprising: administering to a mammal in need thereof a therapeutic amount of a

PPAR.alpha. ligand, and a second agent selected from the group consisting of a **PPAR**.gamma. ligand, an RXR ligand, a **PPAR**.gamma./RXR ligand and Vitamin D or an analog thereof effective to reverse, slow, stop, or prevent the pathological inflammatory and or. . .
37. The method in accordance with claim 36, wherein the **PPAR** .gamma. ligand is a dithiolane derivative.

38. The method in accordance with claim 37, wherein the **PPAR** .gamma. ligand is a dithiolane derivative, said dithiolane derivative is a member selected from the group consisting of formula A, formula. . .
39. The method in accordance with claim 36, wherein said **PPAR** .alpha. ligand is a **PPAR**.alpha. agonist selected from the group consisting of a saturated or unsaturated fatty acid, an eicosanoid, leukotriene or other arachidonic acid. . .

L4 ANSWER 5 OF 14 USPATFULL
AN 2002:55055 USPATFULL
TI Substituted stilbenes as glucose uptake enhancers
IN Patterson, John, Mountain View, CA, UNITED STATES
Park, Sophia Jeong-Weon, Emeryville, CA, UNITED STATES
Lum, Robert T., Palo Alto, CA, UNITED STATES
Spevak, Wayne R., Albany, CA, UNITED STATES
PI US 2002032218 A1 20020314
AI US 2001-872763 A1 20010531 (9)
PRAI US 2000-208591P 20000602 (60)
DT Utility
FS APPLICATION
LREP HELLER EHRMAN WHITE & MCAULIFFE LLP, 275 MIDDLEFIELD ROAD, MENLO PARK, CA, 94025-3506
CLMN Number of Claims: 35
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1544
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compounds of formula I activate the insulin receptor kinase. Pharmaceutical compositions comprising the compounds, and methods of treatment of hyperglycemia and other diseases involving imbalance of glucose levels, especially for the treatment of type II diabetes, by administering these compounds to mannnalian hosts, and processes for their preparation, are also described.
SUMM . . . the effects of insulin, but none appear to act directly on the insulin receptor kinase. For example, thiazolidinediones, such as **pioglitazone**, enhance adipocyte differentiation [Kletzien et al., Mol. Pharmacol. 41:393 (1992). These thiazolidinediones represent a class of potential anti-diabetic compounds that. . . enhance the response of target tissues to insulin [Kobayashi, Diabetes, 41:476 (1992)]. The thiazolidinediones switch on peroxisome proliferator-activated receptor .gamma. (**PPAR**.gamma.), the nuclear transcription factor involved in adipocyte differentiation [Kliewer et al., J. Biol. Chem., 270:12953 (1995)], and do not have. . .
SUMM . . . as anti-virals [Haugwitz et al., PCT International Publication No. WO 9625399]. Tetra-substituted stilbenes, such as tamoxifen, are used in treating **breast cancer** [Furr et al., Pharmacol. Ther. 25:127-205 (1984)]. There is extensive literature describing the use of the stilbenes in the preparation. . .

L4 ANSWER 6 OF 14 USPATFULL
AN 2002:32700 USPATFULL

TI Substituted piperidines as melanocortin receptor agonists
IN Palucki, Brenda L., Hillsborough, NJ, UNITED STATES
Barakat, Khaled J., Brooklyn, NY, UNITED STATES
Guo, Liangqin, Edison, NJ, UNITED STATES
Lai, Yingjie, Edison, NJ, UNITED STATES
Nargund, Ravi P., East Brunswik, NJ, UNITED STATES
Park, Min K., Whippany, NJ, UNITED STATES
Pollard, Patrick G., Oakhurst, NJ, UNITED STATES
Sebhat, Iyassu K., Hoboken, NJ, UNITED STATES
Ye, Zhixiong, Princeton, NJ, UNITED STATES
PI US 2002019523 A1 20020214
AI US 2001-812965 A1 20010320 (9)
PRAI US 2000-191442P 20000323 (60)
US 2000-242265P 20001020 (60)
DT Utility
FS APPLICATION
LREP MERCK AND CO INC, P O BOX 2000, RAHWAY, NJ, 070650907
CLMN Number of Claims: 34
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 4285
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Certain novel substituted piperidine compounds are agonists of the human melanocortin receptor(s) and, in particular, are selective agonists of the human melanocortin-4 receptor (MC-4R). They are therefore useful for the treatment, control, or prevention of diseases and disorders responsive to the activation of MC-4R, such as obesity, diabetes, sexual dysfunction, including erectile dysfunction and female sexual dysfunction.
SUMM . . . rate, reducing fat intake or reducing carbohydrate craving), diabetes mellitus (by enhancing glucose tolerance, decreasing insulin resistance), hypertension, hyperlipidemia, osteoarthritis, **cancer**, gall bladder disease, sleep apnea, depression, anxiety, compulsion, neuroses, insomnia/sleep disorder, substance abuse, pain, male and female sexual dysfunction (including. . .
SUMM . . . points of sexual function. In particular, anatomic and functional modification of such trigger points may diminish the orgasmic potential in **breast cancer** and gynecologic **cancer** patients. Treatment of female sexual dysfunction with an MC-4 receptor agonist can result in improved blood flow, improved lubrication, improved. . .
SUMM [0252] (a) insulin sensitizers including (i) **PPAR**.gamma. agonists such as the glitazones (e.g. troglitazone, **pioglitazone**, englitazone, MCC-555, BR-49653 and the like), and compounds disclosed in WO97/27857, 97/28115, 97/28137 and 97/27847; (ii) biguanides such as metformin. . .
SUMM [0257] (f) **PPAR**.delta. agonists, such as those disclosed in WO97/28149;
SUMM [0260] (i) **PPAR**.alpha. agonists such as described in WO 97/36579 by Glaxo;
SUMM [0261] (j) **PPAR**.gamma. antagonists as described in WO97/10813;

L4 ANSWER 7 OF 14 USPATFULL
AN 2002:12568 USPATFULL
TI METHODS AND PHARMACEUTICAL COMPOSITIONS FOR INHIBITING TUMOR CELL GROWTH
IN SPIEGELMAN, BRUCE M., WABAN, MA, UNITED STATES
ALTIOK, SONER, BOSTON, MA, UNITED STATES
MUELLER, ELISABETTA, BOSTON, MA, UNITED STATES
SARRAF, PASHA, BOSTON, MA, UNITED STATES
TONTONOZ, PETER, SAN DIEGO, CA, UNITED STATES

PA Dana-Farber Cancer Institute (U.S. corporation)
PI US 2002006950 A1 20020117
AI US 1997-923346 A1 19970904 (8)
RLI Continuation of Ser. No. US 1996-766553, filed on 11 Dec 1996, ABANDONED
DT Utility
FS APPLICATION
LREP LAHIVE & COCKFIELD, 28 STATE STREET, BOSTON, MA, 02109
CLMN Number of Claims: 48
ECL Exemplary Claim: 1
DRWN 16 Drawing Page(s)
LN.CNT 2290
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention is based on the finding that activation of **PPAR**.gamma. plays a key role in inducing growth arrest and differentiation of certain actively proliferating cells. We show that administration of **PPAR**.gamma. agonists, such as thiazolidinedione ligands (TZDs), is effective both in vitro and in vivo at inhibiting the proiferation of such cells.

AB The present invention is based on the finding that activation of **PPAR**.gamma. plays a key role in inducing growth arrest and differentiation of certain actively proliferating cells. We show that administration of **PPAR**.gamma. agonists, such as thiazolidinedione ligands (TZDs), is effective both in vitro and in vivo at inhibiting the proiferation of such. . .

SUMM [0003] The peroxisome proliferator-activated receptors, or "**PPAR** ", are members of the type II class of steroid/thyroid superfamily of receptors and which mediate the pleiotropic effects of peroxisome proliferators. Type II class of nuclear receptors includes **PPAR** , the thyroid hormone receptor (T.sub.3R), and the vitamin D.sub.3 receptor (VD.sub.3R). Type II receptors are functionally distinct from the classical. . .

SUMM [0004] The present invention is based on the finding that activation of **PPAR**.gamma. plays a key role in inducing growth arrest by terminal differentiation of actively proliferating **PPAR** .gamma.-expressing cells, particularly transformed adipose precursor cells.

SUMM [0005] Accordly, one aspect of the invention provides a method for inhibiting proliferation of a **PPAR**.gamma.-responsive hyperproliferative cell, comprising ectopically contacting the cell with a a **PPAR**.gamma. agonist in an amount effective to induce differentiation of the cell. For example, the instant method can be used for the treatment of, or prophylactically prevention of a disorder characterized by aberrant cell growth of **PPAR** .gamma.-responsive hyperproliferative cells, e.g., by administering a pharmaceutical preparation of a **PPAR**.gamma. agonist in an amount effective to inhibit growth of the **PPAR** .gamma.-responsive hyperproliferative cells.

SUMM . . . fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic **cancer**, **breast cancer**, ovarian **cancer**, prostate **cancer**, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical **cancer**, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma,

craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic. . .

SUMM [0010] In preferred embodiments, the **PPAR**.gamma. agonist used in the instant method is a ligand of a **PPAR**.gamma. protein which activates a transcriptional activity of the **PPAR**.gamma. protein. For example, the **PPAR**.gamma. agonist can be a thiazolidinedione, or an analog thereof. Exemplary **PPAR**.gamma. agonists include **pioglitazone**, troglitazone, ciglitazone, englitazone, BRL49653, and chemical derivatives thereof. In certain preferred embodiments, the **PPAR**.gamma. agonist is represented in the general formula: ##STR1##

SUMM [0012] In other embodiments, the **PPAR**.gamma. agonist can be a naturally-occurring ligand of the receptor, such as an arachidonate metabolite, e.g., a metabolite of PGD.sub.2.

SUMM . . . side-effects to treatment with a PPARY agonists, it may be desirable in certain embodiments of the subject method that the **PPAR**.gamma. agonist activates **PPAR**.gamma.-dependent transcription at a concentration at least one order of magnitude less than required for the same level of activation of **PPAR**.alpha., **PPAR**.delta. or RaR-dependent transcription.

SUMM [0014] The **PPAR**.gamma. agonist can be administered alone, or as part of a combinatorial therapy. For example, the **PPAR** .gamma. agonist can be conjointly administered with one or more agents such as mitotic inhibitors, alkylating agents, antimetabolites, nucleic acid intercalating agents, topoisomerase inhibitors, agents which promote apoptosis, and/or agents which increase immune responses. In other embodiments, the **PPAR**.gamma. agonist can be conjointly administered with an RxR agonist. Such RxR agonist can be natural or synthetic retinoids. An exemplary. . .

SUMM [0015] Still another aspect of the present invention provides compositions and kits for conjointly administering a **PPAR** .gamma. agonist and an RxR agonist. For example, both agents can be pre-mixed, preferably in a pharmaceutically acceptable carrier. Alternatively, the agents can be provided separately in the form of a kit comprising (i) a first pharmaceutical composition including a **PPAR**.gamma. ligand in a pharmaceutically acceptable carrier, and (ii) a second pharmaceutical composition including an RxR agonists in a pharmaceutically acceptable carrier, the **PPAR**.gamma. and RxR agonists being present in a therapeutically effective amount to, upon conjoint administration, induce terminal differentiation of a **PPAR**.gamma.-responsive hyperproliferative cell in a subject animal.

SUMM [0016] Likewise, the **PPAR**.gamma. agonist useful in the methods of the present invention can be administered conjointly with other agents which effect, e.g., the. . . or immune response against, the hyperproliferative cells to be treated. As above, the secondary agents can be pre-mixed with the **PPAR**.gamma. agonist, or provided as part of a kit comprising (i) a first pharmaceutical composition including a **PPAR**.gamma. ligand in a pharmaceutically acceptable carrier, and (ii) a one or more additional pharmaceutical composition(s) including one or more agents. . .

SUMM [0017] This invention also relates to the surprising discovery that **PPAR**.gamma. is consistently and selectively expressed in each of the major histologic types of human liposarcoma compared to other soft tissue. . . augmenting diagnosis of liposarcomas, comprising detecting in a sample of transformed cells one or both of a diagnostic level of **PPAR**.gamma. mRNA or **PPAR**.gamma. protein, wherein elevated expression of **PPAR**.gamma. mRNA or protein in cells of the sample increases the likelihood that at least a portion of the transformed cells. . .

DRWD [0020] FIG. 1 is a panel of photographs showing the effects of **pioglitazone** in stimulating growth arrest and adipose differentiation of NIH-3T3 cells ectopically expressing **PPAR** .sub.7 (NIH-**PPAR**.gamma.) compared to control cells infected with the empty vector (NIH-vector). Arrow shows a differentiated adipocyte containing lipid drops in the. . .

DRWD [0021] FIGS. 2A, 2B and 2C show graphs depicting the growth of NIH-**PPAR**.gamma., NIH-vector or HIB1B cells in the presence or absence of PPARY ligands. FIG. 2A is a graph depicting the cumulative growth of cells untreated or treated with 5 .mu.M **pioglitazone** . FIG. 2B is a bar graph showing the percent decrease in cell number in the **pioglitazone**-treated plates relative to the untreated plates. FIG. 2C is a bar graph showing exponentially growing cells treated without or with two thiazolidinediones, **pioglitazone** (5 .mu.M) or BRL49653 (1 .mu.M) for 5 days.

DRWD [0022] FIG. 3 is a bar graph showing the effects of transcription factor activity of **PPAR**.gamma. on the negative regulatory function of cell growth. The left panel shows schematic representations of wild type **PPAR**.gamma.1 and 2, or mutant **PPAR**.gamma.2 cDNAs. The right panel shows the effects of **pioglitazone** treatment on the growth rate of cells expressing wild type or mutant forms of PPARY treated with or without **pioglitazone**.

DRWD . . . a variety of human tissues. As indicated to the left of the figure, the blot was hybridized with cDNA for **PPAR**.gamma. and for the adipocyte-specific binding protein aP2.

DRWD [0024] FIG. 5A shows Northern analysis of the expression of **PPAR** .gamma. RNA in RNA prepared from a variety of liposarcomas (SP107, SP144, SP147, SP154, SP158, SP160, SP115, SP155, SP156, SP200, SP204,. . .

DRWD [0025] FIG. 5B shows Northern analysis of the expression of **PPAR** .gamma. RNA in two liposarcomas (SP155 and SP156) compared to a variety of other types of soft tissue sarcomas which include. . . or malignant fibrous histiocytoma (MFH). RNA prepared from fat tissue is shown as a control. The blot was hybridized with **PPAR**.gamma. cDNA.

DRWD . . . with a fusion expression plasmid having the yeast GAL4 DNA binding domain linked to the ligand binding domain of h **PPAR** .gamma.. The level of activation is indicated with respect to the concentration of the thiazolidinedione compounds, BRL 49653 (shown by filled circles), **pioglitazone** (shown by unfilled circles) and troglitazone (shown by filled squares).

DRWD . . . primary cultures of liposarcoma cells cultured in the absence (panels A, C and E) and in the presence of the **PPAR**.gamma. ligand **pioglitazone** (panels B, D and F). Panels A and B represent untreated and treated cells, respectively; panels C and D represent. . .

DRWD . . . 8 is a Northern analysis showing the expression of adipocyte-specific markers in untransfected NIH cells (NIH-vector), NIH cells that express **PPAR**.gamma. from a retroviral vector (NIH-**PPAR**.gamma.) and human liposarcoma cells (LS 857). Indicated are untreated cultures (-) and cultures treated with **pioglitazone** alone (pio), the RXR-specific ligand, LG 268, or both. As indicated to the left, the blot was hybridized with **PPAR**.gamma., aP2 and adipsin.

DRWD [0029] FIG. 9 is a photograph showing the morphological effects of treatment of RXR-or **PPAR**-specific ligands on primary cultures of human liposarcoma cells (LS 857) with the indicated ligands: LG 268, **pioglitazone** (pio), both ligands (pio and LG 268), BRL 49653 alone (BRL), or in combination with LG 268 (BRL and LG. . .

DRWD [0031] FIG. 11 represents a Northern blot demonstrating the expression

of **PPAR**.gamma. sub-types in various human **cancer** cell lines.

DRWD [0032] FIGS. 12 and 13 are graphs depicting the effect of LG 268 ("Ig") and **pioglitazone** ("pio") on the HL-60 (leukemic) cell line.

DRWD [0033] FIG. 14 is a graph depicting the effect of LG 268 ("compound 268") and **pioglitazone** ("pio") on the human prostrate **cancer** cell line PC3.

DETD . . . promising alternative to conventional chemotherapy of certain malignancies. The principle known as "differentiation therapy" is based on the observation that **cancer** cells often seem to be stuck at an immature stage of development. Over the past decade it has been demonstrated. . .

DETD [0035] According to the present invention, receptors of the peroxisome proliferator-activated receptor (**PPAR**) family also represent potential targets for differentiation therapy. As described in greater detail below, agonists of the **PPAR**.gamma. sub-family can be used to inhibit the proliferation of a variety of hyperplastic and neoplastic tissues. In accordance with the present invention, **PPAR**.gamma. agonists can be used in the treatment of both pathologic and non-pathologic proliferative conditions characterized by unwanted growth of **PPAR**.gamma.-responsive cells. Such conditions include tissue having transformed cells, e.g., such as carcinomas, sarcomas and leukemias.

DETD . . . can be carried out by inducing terminal adipocytic differentiation with an agent(s) that causes activation of transcriptional complexes which include **PPAR**.gamma.. The method of the present invention is based in part on the unexpected finding that administration of **PPAR**.gamma. agonists, such as the synthetic thiazolidinedione ligands (TZDs), was effective in reducing the size of adipose cell tumors in vivo. As described in the appended examples, we demonstrate that activation of **PPAR** .gamma. is sufficient to cause cell cycle arrest, as well as to initiate adipogenesis, in logarithmically growing cells. We also describe that **PPAR**.gamma. is expressed consistently in each of the major histologic types of human liposarcoma, and that activation of this receptor with. . .

DETD [0038] In addition to soft tissue lesions, **PPAR**.gamma. agonists can also be used opportunely in the treatment of proliferative disorders involving hematopoietic and lymphatic tissue, as well as. . . describe the expression of PPARY in cells derived from a variety of carcinomas and leukemias. Moreover, we have demonstrated that **PPAR**.gamma. agonists are capable of inhibiting the proliferation of such cells, and have accordingly established a general paradigm by which growth of **PPAR**.gamma.-responsive hyperproliferative cells can be regulated.

DETD [0039] We further demonstrate that RXR-specific ligands are also potent adipogenic agents in cells expressing the **PPAR** .gamma./RXR.alpha. heterodimer, and that simultaneous treatment of liposarcoma cells with both **PPAR**.gamma.- and RXR-specific ligands results in an additive stimulation of differentiation. These results suggest that **PPAR**.gamma. ligands such as thiazolidinediones and RXR-specific retinoids alone or in combination will be useful as differentiation therapy for liposarcoma.

DETD [0041] The term "**PPAR**.gamma." refers to members of the peroxisome proliferator-activated receptors family which are expressed, inter alia, in adipocytic and hematopoietic cells (Braissant,. . . 137(1): 354-66), and which function as key regulators of differentiation. Contemplated within this definition are variants thereof, as for example, **PPAR**.gamma.1 and **PPAR** .gamma.2 which are two isoforms having a different N-terminal generated

by alternate splicing of a primary RNA transcript (Tontonoz, P. et. . .

DETD [0042] The terms "**PPAR**.gamma.-responsive hyperproliferative cell" and "**PPAR**.gamma.-responsive neoplastic cell" are used interchangeably herein and refer to a neoplastic cell which is responsive to **PPAR**.gamma. agonists. This neoplastic cell responds to **PPAR**.gamma. receptor activation by inhibiting cell proliferation and/or inducing the expression of differentiation-specific genes. This term includes tumor-derived cells that differentiate into adipocytic lineages in response to **PPAR**.gamma. ligands, e.g., human liposarcoma cells.

DETD [0043] As used herein, a "**PPAR**.gamma. agonist", that is useful in the method of the invention, refers to an agent which potentiates, induces or otherwise enhances the transcriptional activity of a **PPAR**.gamma. receptor in a neoplastic cell. In certain embodiments, an agonist may induce activation of transcription by **PPAR**.gamma. transcriptional complexes, e.g., such as by mimicking a natural ligand for the receptor. In other embodiments, the agonist potentiates the sensitivity of the receptor to a **PPAR** .gamma. ligand, e.g., treatment with the agonist lowers the concentration of ligand required to induce a particular level of receptor-dependent gene. . .

DETD [0044] As used herein, the term "**PPAR**.gamma. ligand", that is useful in the method of the invention, includes any naturally-occurring or non-naturally occurring agents that selectively and specifically binds to a **PPAR**.gamma. protein and upon binding, activates transcription of genes which contain a **PPAR**.gamma. responsive element. Examples of such ligands include, but are not limited to thiazolidinedione compounds, e.g., **pioglitazone**, troglitazone, BRL49653, and derivatives thereof, or prostaglandin (PG) metabolites, e.g., prostaglandin 15-deoxy-.sup..DELTA.12, 14 PGJ.sub.2, and derivatives thereof.

DETD [0046] The term "activation of **PPAR**.gamma." refers to the ability of a compound to selectively activate **PPAR** .gamma.-dependent gene expression, e.g., by increasing **PPAR** .gamma.-dependent transcription of a gene.

DETD [0047] The "transcriptional activity" of a **PPAR**.gamma. receptor refers to the ability of the receptor, in a ligand-dependent manner, to bind to DNA and, by itself or. . . of RNA polymerase in order to cause transcription of DNA sequences proximate the site on the DNA to which the **PPAR**.gamma. receptor bound. A **PPAR** .gamma. receptor is "transcriptionally activated" when, in a ligand complexed state it causes a higher level of expression of a gene. . .

DETD [0053] As used herein the term "leukemic **cancer**" refers to all cancers or neoplasias of the hemopoietic and immune systems (blood and lymphatic system). The acute and chronic. . . other types of tumors of the blood, bone marrow cells (myelomas), and lymph tissue (lymphomas), cause about 10% of all **cancer** deaths and about 50% of all **cancer** deaths in children and adults less than 30 years old. Chronic myelogenous leukemia (CML), also known as chronic granulocytic leukemia. . .

DETD . . . "antiproliferative agent" are used interchangeably herein and refer to agents that have the functional property of inhibiting the proliferation of **PPAR**.gamma.-responsive cells, e.g., inhibiting the development or progression of a neoplasm having such a characteristic, particularly an adipocytic neoplasm or hematopoietic. .

DETD [0056] As used herein, a "therapeutically effective antineoplastic amount" of a **PPAR**.gamma. agonist refers to an amount of an agent which is effective, upon single or multiple dose administration to

the patient, at inhibiting the growth of neoplastic **PPAR** .gamma.-responsive cells, or in prolonging the survival of the patient with such neoplastic cells beyond that expected in the absence of. . .

DETD [0057] As used herein, "a prophylactically effective antineoplastic amount" of a compound refers to an amount of a **PPAR**.gamma. agonist which is effective, upon single- or multiple-dose administration to the patient, in preventing or delaying the occurrence of the. . .

DETD . . . to at least statistically significant differences between the two states. For example, "an amount effective to inhibit growth of the **PPAR**.gamma.-responsive hyperproliferative cells" means that the rate of growth of the cells will at least statistically significantly different from the untreated. . .

DETD [0060] "Signal transduction of a **PPAR**.gamma. receptor protein" is the intracellular processing of chemical signals that occur as a consequence of activation of the nuclear receptor,. . .

DETD . . . construct will include a reporter gene in operative linkage with one or more responsive elements arranged as direct repeats of **PPAR**.gamma.-response element (PPRE). The activity of at least one or more of these control sequences is directly regulated by the **PPAR**.gamma. nuclear receptor protein. The transcriptional regulatory sequences include the promoter and other regulatory regions, such as enhancer sequences, that modulate the activity of the promoter. For example, activation of the high affinity heterodimer complex of **PPAR**.gamma./RXR with a **PPAR**.gamma. ligand bound to at least one or more PPRE response elements may enhance the activity of the promoter by altering. . .

DETD [0063] In one aspect, this invention features methods for inhibiting the proliferation and/or reversing the transformed phenotype of **PPAR** .gamma.-responsive hyperproliferative cells by contacting the cells with a **PPAR**.gamma. agonist. In general, the method includes a step of contacting pathological hyperproliferative cells with an amount of a **PPAR**.gamma. agonist effective for promoting the differentiation of the hyperproliferative cells. The present method can be performed on cells in culture,. . . out on a human or other animal subject. Induction of terminal differentiation of transformed cells in vivo in response to **PPAR**.gamma. agonists represents a promising alternative to conventional highly toxic regimens of chemotherapy.

DETD [0064] While the **PPAR**.gamma. agonists can be utilized alone, the subject differentiation therapy can be combined with other therapeutics, e.g., such as cell cycle. . . for the treated cells, may be given in smaller doses due to an additive, and sometimes synergistic effect with the **PPAR**.gamma. agonist.

DETD . . . lymphoid, gastrointestinal, and genito-urinary tract as well as adenocarcinomas which include malignancies such as most colon cancers, renal-cell carcinoma, prostate **cancer** and/or testicular tumors, non-small cell carcinoma of the lung, **cancer** of the small intestine and **cancer** of the esophagus. According to the general paradigm of **PPAR**.gamma. involvement in differentiation of transformed cells, exemplary solid tumors that can be treated according to the method of the present invention include sarcomas and carcinomas with **PPAR**.gamma.-responsive phenotypes, such as, but not limited to: fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic **cancer**, **breast cancer**, ovarian **cancer**, prostate **cancer**, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma,

medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical **cancer**, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic. . .

DETD [0069] Particular examples of a non-naturally occurring **PPAR** .gamma. ligand include thiazolidine (TZD) derivatives known as thiazolidinediones, e.g., proglitazone (also known as AD-4833 and U-72107E), troglitazone (also known as. . .

DETD [0070] Particular examples of naturally-occurring **PPAR**.sub.7 ligands include arachidonic acid metabolites, e.g., prostaglandin J.sub.2 (PGJ.sub.2) metabolites, e.g., 15-deoxy-.DELTA..sup.12, 14-prostaglandin J.sub.2. Prostaglandin J2 dehydration and isomerization products,. . .

DETD [0072] In general, it will be preferable to choose a **PPAR** .gamma. agonist which specifically activates that **PPAR** isoform relative to, for example, **PPAR**.alpha. and/or **PPAR** .delta.. According to this present invention, specificity for the **PPAR**.gamma. isoform can reduce unwanted side effects, such as **PPAR**.alpha.-mediated hepatocarcinogenesis. In particular, the **PPAR**.gamma. agonist of the present method preferably activates **PPAR**.gamma.-dependent transcription at a concentration at least 1 order of magnitude less than that which activates **PPAR** .alpha.-dependent transcription, and even more preferably at a concentration at least 2, 3, 4 or 5 orders of magnitude less.

DETD [0073] In one embodiment, the **PPAR**.gamma. agonist is represented by the general formula: ##STR3##

DETD [0098] Compounds useful for practicing the present invention, and methods of making these compounds are known. Examples of **PPAR** .gamma. agonists are disclosed in PCT publications WO 91/07107; WO 92/02520; WO 94/01433; WO 89/08651; WO 95/18533; WO 95/35108; Japanese patent. . .

DETD [0099] Exemplary **PPAR**.gamma. agonist can be selected from amongst such compounds as 5-[4-[2-(5-ethylpyridin-2-yl)ethoxyl]benzyl]thiadiazolidine-2,4-dione: (**pioglitazone**); 5-[4-[(1-methylcyclohexyl)methoxy]benzyl]thiadiazolidine-2,4-dione: (ciglitazone); 5-[(2-benzyl-2,3-dihydrobenzopyran)-5-ylmethyl]thiadiazoline-2,4-dione: (englitazone); 5-[(2-alkoxy-5-pyridyl)methyl]-2,4- thiazolidinedione; 5-[(substituted-3-pyridyl)methyl]-2,4-thiazolidinedione; 5-[4-(2-methyl-2-phenylpropoxy)benzyl]thiazolidine-2,4-dione; 5-[4-[3-(4-methoxyphenyl)-2-oxooxazolidin-5-yl]-methoxy]benzyl-2,4-thiazoli-dinedione; 5-[4-[3-(3,4-difluorophenyl)-2-oxooxazolidin-5-yl]-methoxy]benzyl-2,4-thiazo-lidinedione; 5-[4-[3-(4-chloro-2-fluorophenyl)-2-oxooxazolidin-5-yl]methoxy]benzyl-2,4-thiazolidinedione; 5-[4-[3-(4-trifluoromethoxyphenyl)-2-oxooxazolidin-5-yl]methoxy] benzyl-2,4-thiazolidinedione; 5-[4-[3-(4-trifluoromethylphenyl)-2-oxooxazolidin-5-yl]methoxy]benzyl-2,4-thiazolidinedione; 5-[4-[2-[3-(4-trifluoromethylphenyl)-2-oxooxazolidin-5-yl]ethoxy]benzyl]-2,4-thiazolidinedione; 5-[4-[2-[3-(4-chloro-2-fluorophenyl)-2-oxooxazolidin-5-yl]ethoxy]benzyl]-2,4-thiazolidinedione; 5-[4-[3-(4-pyridyl)-2-oxooxazolidin-5-yl]methoxy]-benzyl-2,4-thiazolidinedione; 5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4- thiazolidinedione: (troglitazone);. . .

DETD [0100] In another embodiment, the subject methods combines the use of **PPAR**.gamma. agonists in combination with one or more RxR-specific ligands. For instance, the subject method can be practiced by conjoint treatment using a **PPAR**.gamma. agonist as described

above and an RxR agonist such as a natural and/or synthetic retinoid. A wide variety of RxR. . . of retinoic acid (c.f., Apfel et al. (1995) JBC 270:30765; Minucci et al. (1996) PNAS 93:1803; Hembree et al. (1996) **Cancer** Res 56:1794; Kizaki et al. (1996) Blood 87:1977; Lemotte et al. (1996) Eur J Biochem 236:328; and U.S. Pat. Nos.. . .

DETD [0104] The subject method may involve, in addition to the use of **PPAR**.gamma. agonist (and optional RxR agonists), one or more other anti-tumor substances. Exemplary combinatorial therapies combining with **PPAR**.gamma. agonists include the use of such as agents as: mitotic inhibitors, such as vinblastine; alkylating agents, such as cisplatin, carboplatin. . .

DETD [0105] Another aspect of the present invention accordingly relates to kits for carrying out the conjoint administeration of the **PPAR** .gamma. agonist with other therapeutic compounds. In one embodiment, the kit comprises a **PPAR**.gamma. agonist formulated in a pharmaceutical carrier, and at least one of an RxR agonist, a mitotic inhibitor, an alkylating agent, an antimetabolite, an nucleic acid intercalating agent, a topoisomerase inhibitor, interferon, formulated with the **PPAR**.gamma. agonist or, as appropriate, in one or more separate pharmaceutical preparations.

DETD [0106] Determination of a therapeutically effective antineoplastic amount and a prophylactically effective antineoplastic amount of a **PPAR**.gamma. agonist, e.g., the design of the differentiation therapy, can be readily made by the physician or veterinarian (the "attending clinician"),. . . bioavailability characteristics of the preparation administered; the dose regimen selected; the kind of concurrent treatment (i.e., the interaction of the **PPAR**.gamma. agonists with other co-administered therapeutics); and other relevant circumstances. U.S. Pat. No. 5,427,916, for example, describes method for predicting the. . .

DETD . . . another aspect, the present invention provides pharmaceutically acceptable compositions which comprise a therapeutically-effective amount of one or more of the **PPAR** .gamma. and/or RXR agonists, formulated together with one or more pharmaceutically acceptable carriers (additives) and/or diluents. As described in detail. . .

DETD [0112] The phrase "therapeutically-effective amount" as used herein means that amount of a **PPAR**.gamma. and/or RXR agonist(s), material, or composition comprising a compound which is effective for producing some desired therapeutic effect by inhibiting. . .

DETD [0113] The phrase "pharmaceutically acceptable" is employed herein to refer to those **PPAR**.gamma. and/or RXR agonists, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use. . .

DETD [0115] The term "pharmaceutically-acceptable salts" refers to the relatively non-toxic, inorganic and organic acid addition salts of **PPAR**.gamma. and/or RXR agonists. These salts can be prepared in situ during the final isolation and purification of the **PPAR** .gamma. and/or RXR agonists, or by separately reacting a purified PPARY and/or RXR agonist in its free base form with a. . .

DETD [0116] In other cases, the **PPAR**.gamma. agonists useful in the methods of the present invention may contain one or more acidic functional groups and, thus, are. . . The term "pharmaceutically-acceptable salts" in these instances refers to the relatively non-toxic, inorganic and organic base addition salts of a **PPAR**.gamma. and/or RXR agonist(s). These salts can likewise be prepared in situ during the final isolation and purification of the **PPAR**.gamma. and/or RXR agonist(s), or by separately reacting the purified **PPAR**.gamma. and/or RXR agonist(s) in its free acid form with a suitable base, such as the hydroxide, carbonate or bicarbonate of. . .

DETD [0120] Methods of preparing these formulations or compositions include

the step of bringing into association a **PPAR**.gamma. and/or RXR agonist(s) with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a **PPAR**.gamma. agonist with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

DETD . . . and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a **PPAR** .gamma. and/or RXR agonist(s) as an active ingredient. A compound may also be administered as a bolus, electuary or paste.

DETD [0127] Suspensions, in addition to the active **PPAR**.gamma. and/or RXR agonist(s) may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose,. . .

DETD . . . for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing one or more **PPAR** .gamma. and/or RXR agonist(s) with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a. . .

DETD [0130] Dosage forms for the topical or transdermal administration of a **PPAR**.gamma. and/or RXR agonist(s) include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active component may be. . .

DETD [0131] The ointments, pastes, creams and gels may contain, in addition to **PPAR**.gamma. and/or RXR agonist(s), excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones,. . .

DETD [0132] Powders and sprays can contain, in addition to a **PPAR** .gamma. and/or RXR agonist(s), excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of. . .

DETD [0133] The **PPAR**.gamma. and/or RXR agonist(s) can be alternatively administered by aerosol. This is accomplished by preparing an aqueous aerosol, liposomal preparation or. . .

DETD [0135] Transdermal patches have the added advantage of providing controlled delivery of a **PPAR**.gamma. and/or RXR agonist(s) to the body. Such dosage forms can be made by dissolving or dispersing the agent in the. . .

DETD [0137] Pharmaceutical compositions of this invention suitable for parenteral administration comprise one or more **PPAR**.gamma. and/or RXR agonist(s) in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions,. . .

DETD [0141] Injectable depot forms are made by forming microencapsule matrices of **PPAR**.gamma. and/or RXR agonist(s) in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature. . .

DETD [0142] When the **PPAR**.gamma. and/or RXR agonist(s) of the present invention are administered as pharmaceuticals, to humans and animals, they can be given per. . .

DETD [0145] The phrases "systemic administration," "administered systemically," "peripheral administration" and "administered peripherally" as used herein mean the administration of a **PPAR** .gamma. and/or RXR agent(s), drug or other material other than directly into the central nervous system, such that it enters the. . .

DETD [0146] These **PPAR**.gamma. and/or RXR agonist(s) may be administered to humans and other animals for therapy by any suitable route of administration, including. . .

DETD [0147] Regardless of the route of administration selected, the **PPAR**.gamma. and/or RXR agonist(s), which may be used in a

suitable hydrated form, and/or the pharmaceutical compositions of the present invention,. . .

DETD [0149] In yet another aspect, detection of **PPAR**.gamma. RNA and/or protein expression can provide a useful diagnostic method for detecting and/or phenotyping hyperplastic and neoplastic cell disroders. For instance, as described in the appended examples, we have observed that **PPAR**.gamma. is selectively expressed in most, if not all liposarcomas, in contrast to undetectable levels of expression found in other forms. . . such as leiomyosarcoma, fibrosarcoma, angiosarcoma, malignant peripheral nerve sheath tumor (MPNS), or malignant fibrous histiocytoma (MFH) (see FIG. 10B). Thus, **PPAR**.gamma. appears to be a sensitive marker for distinguishing adipose cell tumors from other histologic types of soft tissue sarcoma. The amount of specific **PPAR**.gamma. RNA or protein may be measured using any method known to those of skill in the art to be suitable.. . .

DETD [0150] In one embodiment, mRNA is obtained from a sample of cells, and transcripts encoding a **PPAR**.gamma. receptor are detected. To illustrate, an initial crude cell suspension, such as may be obtained from dispersion of a biopsy. . .

DETD . . . probe including a region of nucleotide sequence which is capable of hybridizing to a sense or antisense sequence of a **PPAR**.gamma. transcript. The nucleic acid of a cell is rendered accessible for hybridization, the probe is exposed to nucleic acid of. . .

DETD [0154] In certain embodiments, detection of the **PPAR**.gamma. transcripts utilizes a probe/primer in a polymerase chain reaction (PCR) (see, e.g. U.S. Pat. Nos. 4,683,195 and 4,683,202), such as. . . nucleic acid sample (or optionally a cDNA preparation derived therefrom) with one or more primers which specifically hybridize to a **PPAR** .gamma. transcript under conditions such that hybridization and amplification of at least a portion of the transcript (if present) occurs, and. . .

DETD . . . can be carried out with a probe which, for example, hybridizes under stringent conditions to a nucleic acid encoding a **PPAR** .gamma. transcript. For detection, the probe preferably further comprises a label group attached to the nucleic acid and able to be. . .

DETD [0156] In yet another embodiment, the assay detects the presence or absence of a the **PPAR**.gamma. protein in cells of the cell sample, e.g., by determining the level of the CDK-inhibitory protein by an immunoassay, gel. . .

DETD [0158] In another aspect, the invention features a method for identifying antineoplastic agents which inhibit proliferation of a **PPAR**.gamma.-responsive hyperproliferative cells, e.g., agent which can be used in the above-described method. In any of following drug screening assays, it will be appreciated that selective binding/activation of **PPAR**.gamma. can be assessed by differential screening, e.g., by running a test compound through side-by-side assays which are identical except that **PPAR** .gamma. is replaced by, for example, **PPAR**.alpha., **PPAR** .delta., an RxR receptor or the like. Such assays can be used to select compounds which are selective for the **PPAR**.gamma. sub-type of receptor.

DETD [0159] In one embodiment, the assay includes the steps of: (i) establishing cultures of **PPAR**.gamma.-responsive hyperproliferative cells; (ii) contacting the transformed cells with a test compound; and (iii) detecting one of proliferation and/or differentiation, wherein. . . can be assayed by comparing the number of cells labeled with bromo-deoxy uridine (BrdU) in cultures treated with a potential **PPAR**.gamma. agonist compared to untreated

controls. The extent of, for example, adipocyte differentiation, for example, can be determined by detecting at. . .

DETD [0160] Prior to testing a compound in the cell-based assay, simple binding assays, e.g., using purified or semi-purified **PPAR** .gamma. protein, can be used to isolate those test compounds which at least bind to the receptor. For example, competition binding assays may be performed which comprise incubating the **PPAR**.gamma. receptor protein with a labeled ligand, e.g., [.sup.3H]-TZD, in the absence or the presence of an unlabeled test compound; and. . . ligand, wherein a statistically significant difference in the amount of displaced ligand indicates that the test compound binds specifically to **PPAR**.gamma. (see Lehman et al. (1995) J. Biol. Chem. 270:12953-56). Scatchard analysis may be used to determine the extent of ligand. . .

DETD . . . with a still further embodiment of the present invention, there is provided a method for evaluating whether test compounds are **PPAR**.gamma. ligands by detecting the activation of the **PPAR**.gamma.-signaling pathway, comprising (i) establishing a culture of reagent cells which express **PPAR**.gamma. and include a reporter gene construct having a reporter gene which is expressed in an **PPAR**.gamma.-dependent fashion; (ii) contacting the reaget cells with test compounds; and (iii) monitoring the amount of expression of the reporter gene. Expression of the reporter gene reflects transcriptional activity of the **PPAR**.gamma. protein and, therefore, the presence of an activated receptor **PPAR** .gamma.-ligand complex. In an optional yet preferred embodiment, an apparent **PPAR**.gamma. agonist detected by the transcriptional activation assay can then be further tested by contacting that agent with a **PPAR**.gamma.-responsive hyperproliferative cell.

DETD . . . reporter gene construct will include a reporter gene in operative linkage with one or more transcriptional regulatory elements responsive to **PPAR**.gamma., e.g., such as the **PPAR** .gamma. response element (PPRE) known in the art. The amount of transcription from the reporter gene may be measured using any. . .

DETD [0164] Alternatively, to establish an assay for **PPAR**.gamma. activity without interference from the endogenous receptor, cells can be constructed that express a chimeric protein having the ligand binding domain of **PPAR**.gamma. fused to a DNA binding protein of a heterologous protein, such as the yeast GAL4 DNA binding domain or the. . .

DETD [0165] After identifying certain test compounds as potential **PPAR**.gamma. agonists, the practioner of the subject assay will continue to test the efficacy and specificity of the selected compounds both. . .

DETD **PPAR**.gamma. Induces Cell Cycle Withdrawal

DETD [0170] Preparation of the **PPAR**.gamma.2, **PPAR** .gamma.1, **PPAR**.gamma.-M2, **PPAR**.gamma.-M1 viral expression vectors (Tontonoz, P. et al. (1994) supra; Tontonoz, P. et al. (1994) Cell 79:1147-56) and 3xwt-E2F-Luciferase (Krek, W. et al. (1993) Science 262:1557-60) construct were described previously. The **PPAR**.gamma.2-CD cDNA (encoding amino acids 1-494) was amplified from the **PPAR**.gamma.2 cDNA by PCR and inserted into the pBabe-Puro retroviral expression vector.

DETD [0171] Stable cell lines expressing wild type or mutant forms of **PPAR**.gamma. were derived as described (Tontonoz, P. et al. (1994) Cell 79:1147-56). BOSC23 cells were cultured in 90-mm dishes and transfected. . . cells. NIH-3T3 cell lines infected with empty vector or with viral expression vectors containing wild type or mutant forms of **PPAR**.gamma. cDNA as well as HIBIB and 3T3-F442A cell lines were cultured in DMEM containing 10% cosmic calf serum. **Pioglitazone**

(5-[4-[2-(5-ethyl-2-pyridyl)-ethoxy]benzyl]-2,4-thiazolidinedione) (Upjohn), was dissolved in DMSO and used in cell culture experiments.

DETD [0176] (ii) Activation of **PPAR**.gamma. Leads to Cell Cycle Withdrawal

DETD [0177] To study the effect of **PPAR**.gamma. activation on cell growth, we used a retrovirus transfection system to express **PPAR** .gamma. in NIH3T3 cells. This system allows us to express ectopic genes in many thousands of cells at relatively equal levels. **PPAR** .gamma. has two isoforms, **PPAR**.gamma.1 and **PPAR** .gamma.2, that have different N-terminal formed by alternative splicing (Tontonoz, P. et al. (1994) supra; Zhu, Y. et al. (1993) J. Biol. Chem. 268:26817-20). NIH3T3 fibroblasts were infected with the retroviral expression vector containing cDNA encoding **PPAR**.gamma.1 or 2 (NIH-**PPAR**.gamma.), or with the empty vector (NIH-vector) to create stable cell lines. NIH-**PPAR**.gamma. cells expressed approximately one-third the level of endogenous **PPAR**.gamma. observed in differentiated adipocytes as determined by Northern analysis (data not shown).

DETD [0178] Exponentially growing NIH-**PPAR**.gamma. and NIH-vector cells were treated with a synthetic **PPAR**.gamma. ligand **pioglitazone**, which belongs to the class of thiazolidinedione antidiabetic agents (Lehmann, J.M. et al. (1995) J. Biol. Chem. 270:12953-6). After selection in puromycin, cells were pooled and cultured with or without **pioglitazone** (5 .mu.M) for 5 days. As shown in FIG. 1, treatment with **pioglitazone** at 5 .mu.M concentration had no obvious effect on cells containing empty vectors. In contrast, this agent had dramatic effects on NIH-**PPAR** .gamma. cells, inhibiting cell proliferation and inducing drastic morphological changes. Starting at approximately 48 hours after treatment, increasing numbers of NIH-**PPAR**.gamma. cells changed from the elongated fibroblastic shape to an adipocyte-like morphology, with a round form and accumulation of small drops. . .

DETD [0179] Time course studies at different time points after **pioglitazone** treatment showed that the number of NIH-**PPAR**.gamma. cells in ligand-treated plates was reduced by almost 40% relative to controls by 2 days after treatment and by 80% after 5 days with **pioglitazone** (FIG. 2A, B). The same number of NIH-**PPAR**.gamma., NIH-vector or HIB1B cells were cultured either in the presence (+) or absence (-) of **PPAR**.gamma. ligands. Cell numbers were determined at the indicated time points. The effect of ligands on cell growth is represented as percentage decrease in cell numbers in the treated plates relative to untreated control plates. The growth of **pioglitazone** treated NIH-vector cells decreased by 10% over this period compared to untreated control cells, which may be due to the presence of low amount of **PPAR**.gamma. in these cells (data not shown). The addition of 1 .mu.M BRL49653, another synthetic thiazolidinedione ligand of **PPAR**.gamma. (Lehmann, J. M. et al. (1995) supra) was found to exert the same degree of inhibition on cell growth of NIH-**PPAR**.gamma. cells (FIG. 2C). No obvious cytotoxic effects were observed at the concentrations that we used these compounds.

DETD [0180] To analyze whether **pioglitazone** treatment of cells expressing **PPAR**.gamma. affects progression through a specific cell cycle stage we performed fluorescence activated cell sorting (FACS) analysis and BrdU incorporation experiments.. . . the G0/G1 phase of cell cycle (data not shown). The percentage of cells undergoing DNA synthesis after 5 days of **pioglitazone** treatment was determined by the ability of cells to incorporate BrdU. As shown in table 1, ligand treatment did not change BrdU incorporation rate in NIH-vector cells, but it caused an 80% decrease in the BrdU

incorporation rate in NIH-**PPAR**.gamma. and 3T3-F442A preadipocytes after 5 days of treatment. Together these results demonstrate that ligand activation of **PPAR**.gamma. is sufficient to cause cell cycle withdrawal, even in rapidly proliferating cells. Specifically shown in table 1 are cells cultured on coverslips were untreated or treated with 5 .mu.M **pioglitazone** for 5 days and then pulsed with BrdU for 1 hour. Coverslips were fixed and processed as described in materials. . . two independent experiments in which approximately 400 cells were counted per sample.

TABLE 1

shows the effects of the activation of **PPAR**.gamma. in causing cell cycle withdraw in normal NIH-**PPAR**.gamma. cells, in F442A preadipocytes and in transformed HIB1B cells.

	pioglitazone	BrdU positive %
NIH-vector	-	44
NIH-vector	+	43
NIH-**PPAR**.gamma.	-	44
NIH-**PPAR**.gamma.	+	9
HIB1B	-	75
HIB1B	+	11
3T3-F442A	-	63
3T3-F442A	+	14

DETD [0181] (iii) Transcription Factor Activity is Required for **PPAR**.gamma.-mediated Cell Cycle Withdrawal

DETD [0182] In order to determine some of the structural requirements of **PPAR**.gamma. necessary for growth arrest, NIH3T3 cells were infected with retroviral expression vectors containing wild type or various mutant forms of **PPAR**.gamma. cDNA. Exponentially growing cells were treated for 5 days with **pioglitazone** and cell numbers were determined. As shown in FIG. 3, ligand activation of both **PPAR**.gamma.1 and **PPAR**.gamma.2 induced a similar growth arrest. We also examined an allele of **PPAR**.gamma. (**PPAR**.gamma.-M1) which lacks the N-terminal 127 amino acids of **PPAR**.gamma.2. Previous work has shown that this allele is more active than the wild type with respect to the induction of adipogenesis (Tontonoz, P. and Spiegelman, B. M. (1994) Cell 79:1147-56). Growth inhibition in NIH3T3 cells containing **PPAR**.gamma.-M1 (NIH-M1) was even higher than the cells ectopically expressing wild type **PPAR**.gamma.1 or **PPAR**.gamma.2. To investigate if DNA binding and the transcriptional activation domain of **PPAR** .gamma. are required for its effect on cell growth, NIH3T3 cells were infected with two mutant forms of **PPAR**.gamma.: **PPAR** .gamma.-M2, containing two point mutations in the DNA binding domain and a carboxy-end deleted **PPAR** .gamma.-CD, which lacks the activation domain (AF-2) located in the carboxyl terminal region of all nuclear receptors (reviewed by Mangelsdorf and Evans, 1995). NIH-M2 cells express a **PPAR**.gamma.2 receptor in which cysteine residues at the DNA binding domain at positions 156 and 159 have been changed to serine; NIH--CD cells express a truncated form of **PPAR**.gamma.2 which lacks the conserved carboxyl terminal transactivation domain. Thus, **pioglitazone** treatment did not have any affect on cell growth and adipogenesis in NIH-M2 and NIH--CD cells. Treatment with **pioglitazone** caused about a 10% decrease in cell growth in NIH-vector cells. Cell numbers were determined after 5 days treatment without or with 5 .mu.M **pioglitazone**. Decrease in the cell number in treated plates was represented as relative change

```
L6            0 PPAR AND BREAST (W) CNCER

=> s PPAR AND BREAST (W) CANCER
            339 PPAR
          21798 BREAST
          49897 CANCER
           8003 BREAST (W) CANCER
L7            63 PPAR AND BREAST (W) CANCER

=> S L7 AND PD<1997
        2136598 PD<1997
                  (PD<19970000)
L8             1 L7 AND PD<1997

=> D L8

L8   ANSWER 1 OF 1  USPATFULL
AN      1998:159986  USPATFULL
TI      Phenylacetate and derivatives alone or in combination with other
        compounds against neoplastic conditions and other disorders
IN      Samid, Dvorit, Rockville, MD, United States
PA      The United States of America as represented by the Department of Health
        and Human Services, Washington, DC, United States (U.S. government)
PI      US 5852056              19981222
        WO 9510271  19950420                                          <--
AI      US 1996-633833          19960410 (8)
        WO 1994-US11492         19941012
                                19960410  PCT 371 date
                                19960410  PCT 102(e) date
RLI     Continuation of Ser. No. US 1994-207521, filed on 7 Mar 1994, now
        patented, Pat. No. US 5605930 And Ser. No. US 1993-135661, filed on 12
        Oct 1993, now patented, Pat. No. US 5635532 , each Ser. No. US    - which
        is a continuation-in-part of Ser. No. US 1991-779744, filed on 21 Oct
        1991, now abandoned
DT      Utility
FS      Granted
LN.CNT 5051
INCL    INCLM: 514/510.000
        INCLS: 514/513.000; 514/515.000; 514/529.000; 514/538.000; 514/563.000;
               514/567.000
NCL     NCLM:  514/510.000
        NCLS:  514/513.000; 514/515.000; 514/529.000; 514/538.000; 514/563.000;
               514/567.000
IC      [6]
        ICM: A01N037-12
        ICS: A01N037-44; A61K031-195; A61K031-24
EXF     514/510; 514/513; 514/515; 514/529; 514/538; 514/563; 514/567
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
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HIGHEST APPLICATION PUBLICATION NUMBER: US2002095707
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ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 18 Jul 2002 (20020718/PD)
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          339 PPAR
        21798 BREAST
            1 CNCER
            0 BREAST (W) CNCER
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NEWS 3	Jan 29	FSTA has been reloaded and moves to weekly updates
NEWS 4	Feb 01	DKILIT now produced by FIZ Karlsruhe and has a new update frequency
NEWS 5	Feb 19	Access via Tymnet and SprintNet Eliminated Effective 3/31/02
NEWS 6	Mar 08	Gene Names now available in BIOSIS
NEWS 7	Mar 22	TOXLIT no longer available
NEWS 8	Mar 22	TRCTHERMO no longer available
NEWS 9	Mar 28	US Provisional Priorities searched with P in CA/CAplus and USPATFULL
NEWS 10	Mar 28	LIPINSKI/CALC added for property searching in REGISTRY
NEWS 11	Apr 02	PAPERCHEM no longer available on STN. Use PAPERCHEM2 instead.
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NEWS 14	Apr 09	ZDB will be removed from STN
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NEWS 16	Apr 22	Records from IP.com available in CAPLUS, HCAPLUS, and ZCAPLUS
NEWS 17	Apr 22	BIOSIS Gene Names now available in TOXCENTER
NEWS 18	Apr 22	Federal Research in Progress (FEDRIP) now available
NEWS 19	Jun 03	New e-mail delivery for search results now available
NEWS 20	Jun 10	MEDLINE Reload
NEWS 21	Jun 10	PCTFULL has been reloaded
NEWS 22	Jul 02	FOREGE no longer contains STANDARDS file segment
NEWS 23	Jul 19	NTIS to be reloaded July 28, 2002
NEWS 24	Jul 22	USAN to be reloaded July 28, 2002; saved answer sets no longer valid

NEWS EXPRESS	February 1 CURRENT WINDOWS VERSION IS V6.0d, CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP), AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002
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HIGHEST GRANTED PATENT NUMBER: US6425133
HIGHEST APPLICATION PUBLICATION NUMBER: US2002095707
CA INDEXING IS CURRENT THROUGH 23 Jul 2002 (20020723/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 23 Jul 2002 (20020723/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2002
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substance identification.

=> s lactic acid and benzothiepine?
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        589219 ACID
         28203 LACTIC ACID
                 (LACTIC(W)ACID)
            59 BENZOTHIEPINE?
L1          15 LACTIC ACID AND BENZOTHIEPINE?
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=> d l1 1-15 bib, ab, kwic

L1 ANSWER 1 OF 15 USPATFULL
AN 2002:119900 USPATFULL
TI Combination therapy for the prophylaxis and treatment of hyperlipidemic conditions and disorders
IN Keller, Bradley T., Chesterfield, MO, UNITED STATES

Tremont, Samuel J., St. Louis, MO, UNITED STATES
Glenn, Kevin C., Maryland Heights, MO, UNITED STATES
Manning, Robert E., St. Louis, MO, UNITED STATES
PI US 2002061888 A1 20020523
AI US 2001-802313 A1 20010308 (9)
PRAI US 2000-188378P 20000310 (60)
US 2000-188361P 20000310 (60)
DT Utility
FS APPLICATION
LREP BANNER & WITCOFF, 1001 G STREET N W, SUITE 1100, WASHINGTON, DC, 20001
CLMN Number of Claims: 89
ECL Exemplary Claim: 1
DRWN 5 Drawing Page(s)
LN.CNT 4626
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Novel methods and combinations for the treatment and/or prophylaxis of a hyperlipidemic condition or disorder in a subject, wherein the methods comprise the administration of one or more HMG Co-A reductase inhibitors and one or more ASBT inhibitors selected from the specific group of compounds described herein, and the combinations comprise one or more MIG Co-A reductase inhibitors and one or more of said apical sodium co-dependent bile acid transport inhibitors.
SUMM . . . inhibiting bile acid reabsorption in the ileum recently has been identified. Examples of this class of agents include the substituted **benzothiepines** disclosed in U.S. Pat. 5,994,391. PCT patent application Ser. No. W099/35135 discloses additional substituted benzothiazepine compounds for use as ASBT. . .
DETD . . . sulfuric acid, methanesulfonic acid, acetic acid, formic acid, tartaric acid, maleic acid, malic acid, citric acid, isocitric acid, succinic acid, **lactic acid**, gluconic acid, glucuronic acid, pyruvic acid, oxalacetic acid, fumaric acid, propionic acid, aspartic acid, glutamic acid, benzoic acid, and the. . .

L1 ANSWER 2 OF 15 USPATFULL
AN 2002:54386 USPATFULL
TI Sustained-release preparation
IN Okada, Hiroaki, Osaka, JAPAN
Douken, Yayoi, Osaka, JAPAN
PI US 2002031545 A1 20020314
AI US 2000-520150 A1 20000307 (9)
RLI Continuation of Ser. No. US 1997-962347, filed on 31 Oct 1997, GRANTED, Pat. No. US 6113943
PRAI JP 1996-290441 19961031
DT Utility
FS APPLICATION
LREP Wenderoth Lind & Ponack LLP, 2033 K Street N W, Suite 800, Washington, DC, 20006
CLMN Number of Claims: 16
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1302
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Disclosed is a sustained-release preparation comprising 1) a polymer of **lactic acid** having a weight-average molecular weight of about 25,000 to about 60,000 and 2) a physiologically active substance, and which releases the physiologically active substance over a period of at least about 5 months; the sustained-release preparation shows an almost continuous zero order release of the physiologically active substance over a period of as long as about 5 months.
AB Disclosed is a sustained-release preparation comprising 1) a polymer of

lactic acid having a weight-average molecular weight of about 25,000 to about 60,000 and 2) a physiologically active substance, and which releases. . .

SUMM . . . release of a polypeptide over a period of at least 2 months and containing a copolymer or homopolymer having a **lactic acid**/glycolic acid ratio of 80/20 to 100/0 and having a weight-average molecular weight of 7,000 to 30,000 are described.

SUMM [0006] (1) sustained-release preparation comprising 1) a polymer of **lactic acid** having a weight-average molecular weight of about 25,000 to about 60,000 and 2) a physiologically active substance, and which releases. . .

SUMM [0007] (2) the preparation according to the above (1), wherein the polymer of **lactic acid** is obtained by hydrolyzing a polylactic acid produced by ring-opening polymerization;

SUMM [0008] (3) the preparation according to the above (1), wherein the polymer of **lactic acid** is substantially free from a catalyst;

SUMM [0009] (4) the preparation according to the above (1), wherein the polymer of **lactic acid** has a weight-average molecular weight of about 30,000 to about 50,000;

SUMM [0010] (5) the preparation according to the above (1), wherein the polymer of **lactic acid** has a dispersity of about 1.2 to about 4.0;

SUMM . . . the preparation according to the above (1), wherein the ratio of the physiologically active substance relative to the polymer of **lactic acid** is about 0.01 to about 50% (w/w);

SUMM [0021] (15) the preparation according to the above (1), wherein the physiologically active substance is leuprorelin acetate, the polymer of **lactic acid** has a weight-average molecular weight of about 28,400 to about 47,800, and the preparation releases leuprorelin acetate over a period. . .

SUMM . . . a solution containing a physiologically active substance as an internal aqueous phase and with a solution containing a polymer of **lactic acid** having a weight-average molecular weight of about 25,000 to about 60,000 as an oil phase.

SUMM [0033] The polymer of **lactic acid** used in the present invention is a biodegradable polymer which decomposes in a living body over a period of at least about 5 months and has a free terminal carboxyl group. The present polymer is a homopolymer of **lactic acid**.

SUMM [0034] The weight-average molecular weight of the present polymer of **lactic acid** is about 25,000 to about 60,000, preferably about 27,000 to about 55,000, more preferably about 28,000 to about 50,000. Employment. . .

SUMM [0035] The dispersity (weight-average molecular weight/number-average molecular weight) of the polymer of **lactic acid** used in the present invention is preferably about 1.2 to about 4.0, more preferably about 1.5 to about 3.5.

SUMM [0036] The present polymer of **lactic acid** may be of the L-, D- or DL-configuration, with preference given to the DL-configuration. Regarding the DL-configuration, the ratio of. . .

SUMM [0037] The polymer of **lactic acid** used in the present invention is preferably produced by hydrolyzing a starting polylactic acid produced by ring-opening reaction of a cyclic dimer of **lactic acid** and polymerization.

SUMM . . . and polymerization is a polymer of a high molecular weight region, which is not obtained by a dehydration condensation of **lactic acid** wherein heating is conducted under reduced pressure after addition of a catalyst (JP-A 45920/1981, EP-A 26599), or a method for producing a polymer which is obtained by polymerization of

lactic acid without using a catalyst and is substantially free from a catalyst (JP-A 28521/1986, EP-A 172636). The ring-opening reaction and polymerization (hereafter referred to as ring-opening polymerization) is conducted by a method wherein a cyclic dimer of a **lactic acid** is used and a catalyst is added while heating (e.g. J. H. R. Woodland et. al.; J. Med. Chem., 16,. . .

SUMM . . . polymerization is not especially limited as long as it is larger than the weight-average molecular weight of a polymer of **lactic acid** which is obtained by hydrolysis (about 25,000 to about 60,000)r it ranges, for instance, from about 50,000 to about 200,000,. . .

SUMM [0041] Hydrolysis of a polylactic acid produced by ring-opening polymerization to obtain a polymer of **lactic acid** used in the present invention is conducted in the presence of an acid or a base according to a per. . .

SUMM . . . acid include inorganic acids such as hydrochloric acid, nitric acid, sulfuric acid and phosphoric acid; and organic acids such as **lactic acid**, acetic acid, tartaric acid, citric acid and succinic acid. Examples of the base include alkali metal hydroxides such as sodium. . .

SUMM . . . and the like. Therefore, it is appropriately decided by collecting a part of a polylactic acid and a polymer of **lactic acid** in the hydrolysis process and determining the weight-average molecular weight of the collected polylactic acid and a polymer of **lactic acid**. Duration of hydrolysis is not especially limited but ranges, for instance, from about 1 hour to about 10 days, preferably. . .

SUMM . . . polymerization provides a sustained-release preparation with a large initial burst, the polylactic acid which is hydrolyzed, i.e. the polymer of **lactic acid** used in the present invention provides a sustained-release preparation with a small initial burst.

SUMM . . . solution into water or a mixed solution of water and a water-soluble organic solvent, and separating a precipitated polymer of **lactic acid**.

SUMM . . . water-soluble low-molecular compounds, for instance, those having the weight-average molecular weight of at most 1,000. Use of a polymer of **lactic acid** which is subjected to such refining process enables increasing an entrapment ratio of a physiologically active substance in a production. . .

SUMM [0052] Further, by hydrolyzing and refining a polylactic acid produced by ring-opening polymerization, a polymer of **lactic acid** is produced which is substantially free from a poisonous catalyst which is used in the ring-opening polymerization and exemplified by. . .

SUMM [0117] Examples of the osteogenesis promoters include polypeptides such as BMP, PTH, TGF-.beta. and IGF-1, and (2R,4S)--(--)--N--[4-(diethoxyphosphorylmethyl)phenyl]-1,2,4,5-tetrahydro-4-methyl-7,8-methylenedioxy-5-oxo-3-**benzothiepine**-2-carboxamide, 2-(3-pyridyl)-ethane-1,1-diphosphonic acid and raloxifene.

SUMM . . . not limited as long as it contains fine particles (i.e., microspheres) comprising a physiologically active substance and a polymer of **lactic acid**.

SUMM . . . small particles in which a physiologically active substance in a molecular form is dissolved or dispersed in a polymer of **lactic acid** as a solid solution, etc.

SUMM . . . preparation of the present invention include a sustained-release preparation, wherein the physiologically active substance is leuprorelin acetate, the polymer of **lactic acid** has a weight-average molecular weight of about 28,400 to

about 47,800, and the preparation releases leuprorelin acetate over a period. . .

SUMM . . . a solution containing a physiologically active substance as an internal aqueous phase and with a solution containing a polymer of **lactic acid** as an oil phase. The microencapsulation is conducted by an in-water drying method, a phase separation method, a spray drying. . .

SUMM . . . a solution containing a physiologically active substance as an internal aqueous phase and with a solution containing a polymer of **lactic acid** of the present invention as an oil phase is produced, for example, as described below.

SUMM [0130] An internal aqueous phase thus obtained and a solution (oil phase) containing a polymer of **lactic acid** are mixed to obtain a mixture, which is then subjected to emulsification to yield a w/o emulsion.

SUMM [0131] As the solution (oil phase) containing a polymer of **lactic acid**, a solution may be employed that is prepared by dissolving the polymer of **lactic acid** in an organic solvent. Any organic solvent serves this purpose, as long as it has a boiling point not higher than about 120.degree. C., is hydrophobic and dissolves a polymer of **lactic acid**. Examples of such organic solvent include halogenated hydrocarbons (e.g., dichloromethane, chloroform, chloroethane, dichloroethane, trichloroethane, carbon tetrachloride), fatty acid esters (e.g.,. . .

SUMM [0132] Although varying depending on the kind and molecular weight of the polymer of **lactic acid** and the kind of organic solvent used, the polymer concentration in the organic solvent solution is normally about 0.01 to. . .

SUMM . . . obtained is normally used after sterilizing or dust-cleaning filtration with a filter. Although depending on stability of a polymer of **lactic acid**, a solution containing a polymer of **lactic acid** may be stored in a closed container at room temperature or in a cold place.

SUMM . . . mixing ratio of an aqueous solution containing a physiologically active substance and an organic solvent solution containing a polymer of **lactic acid** is normally about 0.1 to about 1000 parts by weight, preferably about 1 to about 100 parts by weight of. . . used, desired pharmacological action, duration of action and other factors, the ratio of the physiologically active substance to polymer of **lactic acid** is normally about 0.01 to about 50% (w/w), preferably about 0.5 to about 40% (w/w), and especially preferably about 0.1. . .

SUMM . . . internal aqueous phase is finer beyond a certain extent, an interaction between a physiologically active substance and a polymer of **lactic acid** becomes stronger and a release control by a polymer of **lactic acid** depends on biodegradability of the polymer of **lactic acid** to make a long-term release control more accurate, which is preferable.

SUMM . . . agent is gradually added to a w/o emulsion while the emulsion is stirred, to precipitate and solidify a polymer of **lactic acid**. Any coacervating agent can be used, as long as it is a polymeric, mineral oil or vegetable oil compound miscible with the solvent for a polymer of **lactic acid** and that does not dissolve a polymer of **lactic acid** for capsulation. Examples of such coacervating agents include silicon oil, sesame oil, soybean oil, corn oil, cotton seed oil, coconut. . .

DETD . . . Ingelheim, Germany) (hereafter referred to as Polymer F) was hydrolyzed by soaking it in 400 ml of a solution wherein DL-**lactic acid** was diluted with distilled water 1/50 or 1/100 (w/w) times (respectively pH 2.09, pH 2.27) at 60.degree. C.

DETD . . . dried for one day at 40.degree. C. under reduced pressure. Before the organic solvent phase were solidified completely, polymer of **lactic acid** was foamed by adjusting the degree of vacuum to enlarge the volume of the polymer of **lactic acid** and then promote evaporation of dichloromethane. The foamed substance obtained was pulverized to yield polymers shown in Table 1.

TABLE 1

Lactic acid conc. (w/w)	Hydrolyzation time (day)	Weight-average molecular weight	Yield (%)	Polymer
1/50	2	47,800	96.6	A
1/100	3	31,200	82.7	B

1/50. . .

DETD . . . the same manner as in Reference Example 1, Polymer F was hydrolyzed to yield polymers shown in Table 2.

TABLE 2

Lactic acid conc. (w/w)	Hydrolyzation time (day)	Weight-average molecular weight	Yield (%)	Polymer
1/50	1.1	69,200	59.3	D
1/50	1.2	62,300	--	E

CLM What is claimed is:

1. Sustained-release preparation comprising 1) a polymer of **lactic acid** having a weight-average molecular weight of about 25,000 to about 60,000 and 2) a physiologically active substance, and which releases. . .

2. The preparation according to claim 1, wherein the polymer of **lactic acid** is obtained by hydrolyzing a polylactic acid produced by ring-opening polymerization.

3. The preparation according to claim 1, wherein the polymer of **lactic acid** is substantially free from a catalyst.

4. The preparation according to claim 1, wherein the polymer of **lactic acid** has a weight-average molecular weight of about 30,000 to about 50,000.

5. The preparation according to claim 1, wherein the polymer of **lactic acid** has a dispersity of about 1.2 to about 4.0.

. . . 14. The preparation according to claim 1, wherein the ratio of the physiologically active substance relative to the polymer of **lactic acid** is about 0.01 to about 50% (w/w).

15. The preparation according to claim 1, wherein the physiologically active substance is leuprorelin acetate, the polymer of **lactic acid** has a weight-average molecular weight of about 28,400 to about 47,800, and the preparation releases leuprorelin acetate over a period. . .

. . . a solution containing a physiologically active substance as an internal aqueous phase and with a solution containing a polymer of **lactic acid** having a weight-average molecular weight of about 25,000 to about 60,000 as an oil phase.

L1 ANSWER 3 OF 15 USPATFULL
AN 2002:51002 USPATFULL
TI Benzothiepin derivatives, process for the preparation of the same and uses thereof
IN Yasuma, Tsuneo, Ibaraki, JAPAN
Makino, Haruhiko, Hyogo, JAPAN
Mori, Akira, Amagasaki, JAPAN
PA Takeda Chemical Industries, Ltd., Osaka, JAPAN (non-U.S. corporation)
PI US 6355672 B1 20020312
WO 2000008018 20000217
AI US 2001-744857 20010130 (9)
WO 1999-JP4269 19990806
20010130 PCT 371 date
PRAI JP 1998-225065 19980807
DT Utility
FS GRANTED
EXNAM Primary Examiner: Solola, T. A.; Assistant Examiner: D'Souza, Andrea
LREP Chao, Mark, Ramesh, Elaine M.
CLMN Number of Claims: 13
ECL Exemplary Claim: 1
DRWN 0 Drawing Figure(s); 0 Drawing Page(s)
LN.CNT 1497
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention provides compounds of the formula: ##STR1##

wherein the ring A is an optionally substituted benzene ring; R.sup.1 is an optionally substituted non-aromatic heterocyclic group; R.sup.2 and R.sup.3 are independently hydrogen atom or an optionally substituted hydrocarbon group; n is an integer of 0-3; or salts thereof, which are useful as medicines having an osteogenesis promoting effect and chondrogensis promoting effect.

The present invention relates to an amine compound having an excellent effect of inhibiting production and/or secretion of amyloid-b protein, a production and use thereof. Especially, it is effective for preventing and/or treating, for example, neurodegenerative diseases, amyloid angiopathy, neurological disorders caused by cerebrovascular disorders, and so forth.

SUMM The present invention relates to **benzothiepine** derivatives having an osteogenesis promoting effect and a chondrogenesis promoting effect, to a process for producing the same, and to. . .

SUMM So far it has been reported that **benzothiepine** derivatives have an osteogenesis promoting effect (Japanese Unexamined Patent Publication No. (hereinafter referred to as JP-A) 3-232880/1991; JP-A 4-364179/1992; JP-A. . .

SUMM The present inventors synthesized a variety of **benzothiepine** derivatives and worked diligently to investigate the biological activity and pharmacological behavior of these derivatives. As a result, they discovered. . .

SUMM . . . heterocyclic group; R.sup.2 is a hydrogen atom or hydrocarbon group which may have a substituent] at the 2 position of **benzothiepine** structure exhibit an excellent osteogenesis promoting effect and a chondrogenesis promoting effect and are superior in oral absorption. The present. . .

SUMM (10) N-[4-(4-morpholinylmethyl)phenyl]-1,2,4,5-tetrahydro-7,8-methylenedioxy-4-methyl-5-oxo-3-**benzothiepine**-2-carboxamide,

SUMM N-[4-(2,4-dioxothiazolidin-5-ylmethyl)phenyl]-1,2,4,5-tetrahydro-7,8-methylenedioxy-4-methyl-5-oxo-3-**benzothiepine**-2-carboxamide, or

SUMM N-[4-(2,4-dioxo-oxazolidin-5-ylmethyl)phenyl]-1,2,4,5-tetrahydro-7,8-

methylenedioxy-4-methyl-5-oxo-3-**benzothiepine**-2-carboxamide, or a salt thereof,

SUMM . . . method for preparing sustained-release preparations, as described in JP-A 9-263545/1997, comprises dispersing Compound (I) into an aliphatic polyester such as **lactic acid**-glycolic acid copolymer according to the in-water drying method, phase separation method, spray drying method, and the like. The sustained-release preparations. . .

DETD Preparation of 6-Hydroxy-8-methoxy-5-oxo-1,2,4,5-tetra-hydro-3-**benzothiepine**-2-carboxylic Acid

DETD . . . off and the resulting residue was applied to silica gel column chromatography. Elution with ethyl acetate/n-hexane (1:2, v/v) afforded methyl 6,8-dimethoxy-5-oxo-1,2,4,5-tetrahydro-3-**benzothiepine** -2-carboxylate (9.5 g, 61%) as a brown oil.

DETD To a solution of methyl 6,8-dimethoxy-5-oxo-1,2,4,5-tetrahydro-3-**benzothiepine**-2-carboxylate (8.5 g) in di-chloromethane (200 ml) was added boron tribromide (1M-di-chloromethane solution, 28.7 ml) under cooling at -78.degree. C., and. . . saturated brine, then dried (MgSO.sub.4), and evaporated. The residue was purified by silica gel column chromatography (AcOEt/n-hexane=v/v=1/3) to give methyl 6-hydroxy-8-methoxy-5-oxo-1,2,4,5-tetrahydro-3-**benzothiepine** -2-carboxylate as colorless crystals (3.5 g, 43%).

DETD A mixture of methyl 6-hydroxy-8-methoxy-5-oxo-1,2,4,5-tetrahydro-3-**benzothiepine**-2-carboxylate (1.0 g), 2N-potassium hydroxide aqueous solution (4 ml) and THF (30 ml) was stirred at 70.degree. C. for 2 hours,. . .

DETD Preparation of (2R,4S)-N-[4-(2,4-Dioxothiazolidin-5-yl-methyl)phenyl]-1,2,4,5-tetrahydro-7,8-methylenedioxy-4-methyl-5-oxo-3-**benzothiepine**-2-carboxamide

DETD A solution of (2R,4S)-(-)-1,2,4,5-tetrahydro-7,8-methylenedioxy-4-methyl-5-oxo-3-**benzothiepine**-2-carboxylic acid (0.28 g), 5-(4-aminobenzyl)-2,4-dioxothiazolidine (0.233 g), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.288 g) and 1-hydroxybenzotriazole (HOBt)(0.162 g) in N,N-dimethylformamide (DMF)(10 ml) was stirred. . .

DETD Preparation of (2R,4S)-N-[4-(Hydantoin-3-ylmethyl)phenyl]-1,2,4,5-tetrahydro-7,8-methylenedioxy-4-methyl-5-oxo-3-**benzothiepine** -2-carboxamide

DETD A solution of (2R,4S)-(-)-1,2,4,5-tetrahydro-7,8-methylenedioxy-4-methyl-5-oxo-3-**benzothiepine**-2-carboxylic acid (0.40 g), 3-(4-aminobenzyl)hydantoin (0.233 g), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.288 g) and HOBt(0.162 g) in DMF (10 ml) was stirred at. . .

DETD Preparation of (2R,4S)-N-[4-(2,4-Dioxothiazolidin-3-yl-methyl)phenyl]-1,2,4,5-tetrahydro-7,8-methylenedioxy-4-methyl-5-oxo-3-**benzothiepine**-2-carboxamide

DETD A solution of (2R,4S)-(-)-1,2,4,5-tetrahydro-7,8-methylenedioxy-4-methyl-5-oxo-3-**benzothiepine**-2-carboxylic acid (0.589 g), 3-(4-aminobenzyl)-2,4-dioxothiazolidine (0.470 g), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.805 g) and HOBt(0.426 g) in DMF (30 ml) was stirred at. . .

DETD Preparation of (2R,4S)-N-[4-(4-Morpholinylmethyl)phenyl]-1,2,4,5-tetrahydro-7,8-methylenedioxy-4-methyl-5-oxo-3-**benzothiepine** -2-carboxamide

DETD A solution of (2R,4S)-(-)-1,2,4,5-tetrahydro-7,8-methylenedioxy-4-methyl-5-oxo-3-**benzothiepine**-2-carboxylic acid (0.400 g), 4-(4-aminobenzyl)morpholine (0.290 g), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.550 g) and HOBt(0.290 g) in DMF (15 ml) was stirred at. . .

DETD Preparation of (2R,4S)-N-[4-(2,6-Dioxo-1-piperidinyl-methyl)phenyl]-

1,2,4,5-tetrahydro-7,8-methylenedioxy-4-methyl-5-oxo-3-**benzothiepine**-2-carboxamide

DETD A solution of (2R,4S)-(-)-1,2,4,5-tetrahydro-7,8-methylenedioxy-4-methyl-5-oxo-3-**benzothiepine**-2-carboxylic acid (0.330 g), 1-(4-aminobenzyl)glutarimide (0.300 g), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.52 g) and HOBt(0.240 g) in DMF (20 ml) was stirred at. . .

DETD Preparation of (2R,4S)-N-[4-(1-Methylhydantoin-3-ylmethyl)-phenyl]-1,2,4,5-tetrahydro-7,8-methylenedioxy-4-methyl-5-oxo-3-**benzothiepine**-2-carboxamide

DETD A solution of (2R,4S)-(-)-1,2,4,5-tetrahydro-7,8-methylenedioxy-4-methyl-5-oxo-3-**benzothiepine**-2-carboxylic acid (0.302 g), 3-(4-aminobenzyl)-1-methylhydantoin (0.213 g), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.228 g) and HOBt(0.160 g) in DMF (6 ml) was stirred at. . .

DETD Preparation of (2R,4S)-N-[4-(2,4-Dioxo-oxazolidin-3-yl-methyl)phenyl]-1,2,4,5-tetrahydro-7,8-methylenedioxy-4-methyl-5-oxo-3-**benzothiepine**-2-carboxamide

DETD A solution of (2R,4S)-(-)-1,2,4,5-tetrahydro-7,8-methylenedioxy-4-methyl-5-oxo-3-**benzothiepine**-2-carboxylic acid (0.320 g), 1-(4-aminobenzyl)-2,4-dioxo-oxazolidine (0.215 g), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.239 g) and HOBt(0.169 g) in DMF (20 ml) was stirred at. . .

DETD Preparation of (2R,4S)-N-[4-(Succinimdomethyl)phenyl]-1,2,4,5-tetrahydro-7,8-methylenedioxy-4-methyl-5-oxo-3-**benzothiepine**-2-carboxamide

DETD A solution of (2R,4S)-(-)-1,2,4,5-tetrahydro-7,8-methylenedioxy-4-methyl-5-oxo-3-**benzothiepine**-2-carboxylic acid (0.70 g), 1-(4-aminobenzyl)succinimide (0.51 g), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.37 g) and HOBt(0.58 g) in DMF (20 ml) was stirred at. . .

DETD Preparation of (2R,4S)-N-[4-(2-Oxazolidon-3-ylmethyl)-phenyl]-1,2,4,5-tetrahydro-7,8-methylenedioxy-4-methyl-5-oxo-3-**benzothiepine**-2-carboxamide

DETD A solution of (2R,4S)-(-)-1,2,4,5-tetrahydro-7,8-methylenedioxy-4-methyl-5-oxo-3-**benzothiepine**-2-carboxylic acid (0.400 g), 3-(4-aminobenzyl)-2-oxazolidone (0.279 g), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.307 g) and HOBt(0.217 g) in DMF (6 ml) was stirred at. . .

DETD Preparation of (2R,4S)-N-[4-(2,4-Dioxo-oxazolidin-5-yl-methyl)phenyl]-1,2,4,5-tetrahydro-7,8-methylenedioxy-4-methyl-5-oxo-3-**benzothiepine**-2-carboxamide

DETD A solution of (2R,4S)-(-)-1,2,4,5-tetrahydro-7,8-methylenedioxy-4-methyl-5-oxo-3-**benzothiepine**-2-carboxylic acid (0.400 g), 5-(4-aminobenzyl)-2,4-dioso-oxazolidine (0.300 g), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.550 g) and HOBt(0.290 g) in DMF (20 ml) was stirred at. . .

DETD Preparation of (2R,4S)-N-[4-(3,5-Dioxo-1,2,4-oxadiazolidin-2-ylmethyl)phenyl]-1,2,4,5-tetrahydro-7,8-methylenedioxy-4-methyl-5-oxo-3-**benzothiepine**-2-carboxamide

DETD A solution of (2R,4S)-(-)-1,2,4,5-tetrahydro-7,8-methylenedioxy-4-methyl-5-oxo-3-**benzothiepine**-2-carboxylic acid (0.28 g), 2-(4-aminobenzyl)-3,5-dioxo-1,2,4-oxadi-azolidine (0.200 g), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (0.228 g) and HOBt(0.141 g) in DMF (6 ml) was stirred at. . .

DETD Preparation of (2R,4S)-N-[4-(1,1-Dioxotetrahydro-2H-1-iso-thiazol-2-ylmethyl)phenyl]-1,2,4,5-tetrahydro-7,8-methyl-enedioxy-4-methyl-5-oxo-3-**benzothiepine**-2-carboxamide

DETD A solution of (2R,4S)-(-)-1,2,4,5-tetrahydro-7,8-methylenedioxy-4-methyl-5-oxo-3-**benzothiepine**-2-carboxylic acid (0.28 g),

2-(4-aminobenzyl)-1,1-dioxotetrahydro-2H-1-isothiazole (0.210 g), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (0.207 g) and HOBt(0.141 g) in DMF (10 ml) was stirred at. . .

DETD Preparation of (2R,4S)-N-[4-(1-Pyrrolidinylmethyl)phenyl]-1,2,4,5-tetrahydro-7,8-methylenedioxy-4-methyl-5-oxo-3-**benzothiepine**-2-carboxamide

DETD A solution of (2R,4S)-(-)-1,2,4,5-tetrahydro-7,8-methylenedioxy-4-methyl-5-oxo-3-**benzothiepine**-2-carboxylic acid (0.28 g), 1-(4-aminobenzyl)pyrrolidine (0.194 g), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.383 g) and HOBt(0.203 g) in DMF (10 ml) was stirred at. . .

DETD Preparation of (2R,4S)-N-[4-(1-Piperidinylmethyl)phenyl]-1,2,4,5-tetrahydro-7,8-methylenedioxy-4-methyl-5-oxo-3-**benzothiepine**-2-carboxamide

DETD A solution of (2R,4S)-(-)-1,2,4,5-tetrahydro-7,8-methylenedioxy-4-methyl-5-oxo-3-**benzothiepine**-2-carboxylic acid (0.28 g), 1-(4-aminobenzyl)piperidine (0.190 g), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.383 g) and HOBt(0.203 g) in DMF (15 ml) was stirred at. . .

DETD Preparation of (2R,4S)-N-Methyl-N-[4-(4-morpholinylmethyl)-phenyl]-1,2,4,5-tetrahydro-7,8-methylenedioxy-4-methyl-5-oxo-3-**benzothiepine**-2-carboxamide

DETD To a solution of (2R,4S)-(-)-1,2,4,5-tetrahydro-7,8-methylenedioxy-4-methyl-5-oxo-3-**benzothiepine**-2-carboxylic acid (0.281 g) and DMF (3 drops) in tetrahydrofuran (THF)(10 ml) was added oxalyl chloride (0.13 ml) under ice cooling,. . .

DETD Preparation of (2R,4S)-N-[4-(1,3-Thiazolidin-3-ylmethyl)-phenyl]-1,2,4,5-tetrahydro-7,8-methylenedioxy-4-methyl-5-oxo-3-**benzothiepine**-2-carboxamide

DETD A solution of (2R,4S)-(-)-1,2,4,5-tetrahydro-7,8-methylenedioxy-4-methyl-5-oxo-3-**benzothiepine**-2-carboxylic acid (0.433 g), 1-(4-aminobenzyl)thiazolidine (0.295 g), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.305 g) and HOBt(0.21 g) in DMF (6 ml) was stirred at. . .

DETD Preparation of (2R,4S)-N-[4-(4-Thiomorpholinylmethyl)-phenyl]-1,2,4,5-tetrahydro-7,8-methylenedioxy-4-methyl-5-oxo-3-**benzothiepine**-2-carboxamide

DETD A solution of (2R,4S)-(-)-1,2,4,5-tetrahydro-7,8-methylenedioxy-4-methyl-5-oxo-3-**benzothiepine**-2-carboxylic acid (0.405 g), 1-(4-aminobenzyl)thiomorpholine (0.313 g), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.307 g) and HOBt(0.21 g) in DMF (12 ml) was stirred at. . .

DETD Preparation of (2R,4S)-N-[4-(4-Oxo-1-piperidinylmethyl)-phenyl]-1,2,4,5-tetrahydro-7,8-methylenedioxy-4-methyl-5-oxo-3-**benzothiepine**-2-carboxamide

DETD A solution of (2R,4S)-(-)-1,2,4,5-tetrahydro-7,8-methylenedioxy-4-methyl-5-oxo-3-**benzothiepine**-2-carboxylic acid (0.433 g), 1-(4-aminobenzyl)-4-oxopiperidine (0.39 g), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.37 g) and HOBt(0.26 g) in DMF (10 ml) was stirred at. . .

DETD Preparation of N-[4-[(2,4-Dioxo-1,3-thiazolidin-5-yl)-methyl]phenyl]-6-hydroxy-8-methoxy-5-oxo-1,2,4,5-tetrahydro-3-**benzothiepine**-2-carboxamide

DETD To a solution of 6-hydroxy-8-methoxy-5-oxo-1,2,4,5-tetrahydro-3-**benzothiepine**-2-carboxylic acid (0.134 g), 5-(4-aminobenzyl)-2,4-dioxo-1,3-thiazolidine (0.12 g), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.192 g) in DMF (5 ml) was added 1-hydroxybenzotriazole (HOBt) (0.10. . .

CLM What is claimed is:

10. N-[4-(4-Morpholinylmethyl)phenyl]-1,2,4,5-tetrahydro-7,8-

methylenedioxy-4-methyl-5-oxo-3-**benzothiepine**-2-carboxamide, N-[4-(2,4-dioxothiazolidin-5-ylmethyl)-phenyl]-1,2,4,5-tetrahydro-7,8-methylenedioxy-4-methyl-5-oxo-3-**benzothiepine**-2-carboxamide, or N-[4-(2,4-dioxo-oxazolidin-5-ylmethyl)phenyl]-1,2,4,5-tetrahydro-7,8-methylenedioxy-4-methyl-5-oxo-3-**benzothiepine**-2-carboxamide, or a salt thereof.

L1 ANSWER 4 OF 15 USPATFULL
AN 2002:32739 USPATFULL
TI Amidino compound and salts thereof useful as nitric oxide synthase inhibitors
IN Webber, Ronald Keith, St. Charles, MO, UNITED STATES
Durley, Richard C., Chesterfield, MO, UNITED STATES
Awasthi, Alok K., Skokie, IL, UNITED STATES
Bergmanis, Arija A., Des Plaines, IL, UNITED STATES
Ganser, Scott S., Chicago, IL, UNITED STATES
Hagen, Timothy J., Gurne, IL, UNITED STATES
Hallinan, E. Ann, Evanston, IL, UNITED STATES
Hansen, Donald W., JR., Skokie, IL, UNITED STATES
Hickory, Brian S., Wildwood, MO, UNITED STATES
Moormann, Alan E., Weldon Springs, MO, UNITED STATES
Pitzele, Barnett S., Skokie, IL, UNITED STATES
Promo, Michelle A., Chesterfield, MO, UNITED STATES
Schartman, Richard R., Evanston, IL, UNITED STATES
Snyder, Jeffrey S., Manchester, MO, UNITED STATES
Trivedi, Mahima, Glenview, IL, UNITED STATES
Tsymbalov, Sofya, Skokie, IL, UNITED STATES
PI US 2002019563 A1 20020214
US 6403830 B2 20020611
AI US 2001-816577 A1 20010323 (9)
PRAI US 2000-191923P 20000324 (60)
DT Utility
FS APPLICATION
LREP Pharmacia Corporation, Corporate Patent Department, P.O. Box 5110, Chicago, IL, 60680-9889
CLMN Number of Claims: 39
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 3313
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to S-[2-[(1-Iminoethyl)amino]ethyl]-2-methyl-L-cysteine, or a pharmaceutically acceptable salt thereof.
SUMM . . . invention, the present inventive compounds can be used in therapeutic combination with an antihyperlipidemic or cholesterol-lowering drug such as a **benzothiepine** or a benzothiazepine antihyperlipidemic drug. Examples of **benzothiepine** antihyperlipidemic drugs useful in the present inventive therapeutic combination can be found in U.S. Pat. No. 5,994,391, herein incorporated by. . .
SUMM . . . spiro systems wherein the cycloalkyl ring has a carbon ring atom in common with the seven-membered heterocyclic ring of the **benzothiepine**.
DETD . . . 28.42 6.3 12.26 19.6
.5 (CaCl.sub.2)
1.5 (H.sub.2O)
(HCl)

##STR97## C.sub.8H.sub.17N.sub.3O.sub.2S
C.sub.3H.sub.6O.sub.3 HCl 38.2 6.99 12.15 10.25 38.32 7.16

12.23 10.81
Lactic Acid

##STR98## C.sub.8H.sub.17N.sub.3O.sub.2S .5
(C.sub.4H.sub.6O.sub.4) HCl .5 (H.sub.2O) 37.09 6.85 12.98 10.95
37.22 6.68 13.08 11.45
Succinic Acid
DETD . . . 8.54 18.08 28.72 6.32 10.10 8.96 18.12
H.sub.2O
D *0.3A *1.6 HCl *1.25 29.34 6.56 11.40 15.39 14.53 29.17
6.71 11.50 15.48 14.51
H.sub.2O
L-(+)-**Lactic Acid**
D *1.0A *1.0 H.sub.2O 40.36 7.70 12.83 9.79 40.79 7.84
12.60 9.68
D *1.0A *1.0 H.sub.2O *1.0 HCl 38.20 6.99 12.15 10.25. . .

L1 ANSWER 5 OF 15 USPATFULL
AN 2002:24062 USPATFULL
TI Apatite-coated solid composition
IN Saito, Kazuhiro, Suita, JAPAN
Hoshino, Tetsuo, Osaka, JAPAN
PA Takeda Chemical Industries, Ltd., Osaka, JAPAN (non-U.S. corporation)
PI US 6344209 B1 20020205
WO 9847485 19981029
AI US 1999-403414 19991020 (9)
WO 1998-JP1870 19980423
19991020 PCT 371 date
PRAI JP 1997-106918 19970424
DT Utility
FS GRANTED
EXNAM Primary Examiner: Page, Thurman K.; Assistant Examiner: Fubara, Blessing
LREP Chao, Mark, Ramesh, Elaine M.
CLMN Number of Claims: 15
ECL Exemplary Claim: 1
DRWN 6 Drawing Figure(s); 4 Drawing Page(s)
LN.CNT 1519
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB An apatite-coated solid composition which contains a biodegradable polymer and an apatite-coated solid composition which contains a biodegradable polymer and a medicinal substance have properties of sustained release and of osteoconductive activity.
DETD . . . include fatty acid polyesters such as polymers, copolymers and their mixture of one or more kinds of .alpha.-hydroxycarboxylic acids (e.g., **lactic acid**, glycolic acid, 2-hydroxybutyric acid, 2-hydroxyvaleric acid, 2-hydroxy-3-methylbutyric acid, 2-hydroxycaproic acid, 2-hydroxyisocaproic acid, 2-hydroxycaprylic acid), hydroxydicarboxylic acids (e.g., malic acid) and hydroxytricarboxylic acids (e.g., malic acid), **lactic acid** caprolactones, valerolactones, etc., and derivatives thereof (e.g., block polymers of polylactic acid, polyglycolic acid and polyethylene glycol), poly-.alpha.-cyanoacrylates, poly-.beta.-hydroxybutyric acid,. . .
DETD . . . synthesized from one or more kinds of .alpha.-hydroxycarboxylic acids are preferred. Specifically, copolymers synthesized from one or more kinds of **lactic acid**, glycolic acid, 2-hydroxybutyric acid, 2-hydroxyvaleric acid etc., or mixtures thereof are used.
DETD Homopolymers of the above-mentioned .alpha.-hydroxycarboxylic acids include homopolymers of **lactic acid**, glycolic acid

and 2-hydroxybutyric acid. The preferable .alpha.-hydroxycarboxylic acid is **lactic acid**. Copolymers of the above-mentioned .alpha.-hydroxycarboxylic acids include copolymers of glycolic acid and the other .alpha.-hydroxycarboxylic acids. Preferable .alpha.-hydroxycarboxylic acids are **lactic acid** and 2-hydroxybutyric acid. Specifically, useful copolymers include **lactic acid**-glycolic acid copolymers and 2-hydroxybutyric acid-glycolic acid copolymers, with preference given to polylactic acid-polyglycolic acid copolymers, etc.

DETD The lower limit of the weight-average molecular weight of a **lactic acid** homopolymer (hereinafter also referred to as polylactic acid) is preferably about 5,000, preferably about 6,000.

DETD The upper limit of the weight-average molecular weight of a **lactic acid** homopolymer is preferably about 10,000,000, more preferably about 5,000,000. Still more preferably about 100,000, especially preferably 50,000.

DETD The content ratio of **lactic acid** and glycolic acid in a polylactic acid or a **lactic acid**-glycolic acid copolymer is preferably from about 100/0 to 50/50 (w/w). The weight-average molecular weight of the **lactic acid** -glycolic acid copolymer is preferably about 5,000 to 100,000, more preferably about 8,000 to 50,000. The **lactic acid** -glycolic acid copolymer can be synthesized by a commonly known production method such as that described in European Patent Application Publication. . .

DETD . . . vitamin D derivatives, vitamin K.sub.2 derivatives, eicosapentaenic acid derivatives, benzylphosphonic acid derivatives, bisphosporic acid derivatives, sex hormone derivatives, phenolsulfophthalein derivatives, **benzothiepine** derivatives, menatetrenone derivatives, helioxanthin derivatives, etc. and peptide osteoinductive factors such as bone morphogenetic protein (BMP) or its derivatives, cartilage. . .

DETD Useful non-peptide osteogenetic promoting substances of the present invention include the sulfur-containing heterocyclic compounds such as (2R,4S)-(-)-N-[4-(Diethoxyphosphorylmethyl)phenyl]-1,2,4,5-tetrahydro-4-methyl-7,8-methylenedioxy-5-oxo-3-**benzothiepine**-2-carboxamide or salts thereof described in U.S. Pat. No. 5,071,841 (Japanese Patent Application Laid-open No. 3-232880), U.S. Pat. No. 5,158,943 (Japanese. . .

DETD Most preferably, the compound (II) is, for example, (2R,4S)-(-)-N-[4-(diethoxyphosphorylmethyl)phenyl]-1,2,4,5-tetrahydro-4-methyl-7,8-methylenedioxy-5-oxo-3-**benzothiepine**-2-carboxamide (hereinafter also referred to as Compound A).

DETD (2R,4S)-(-)-N-[4-(diethoxyphosphorylmethyl)phenyl]-1,2,4,5-tetrahydro-4-methyl-7,8-methylenedioxy-5-oxo-3-**benzothiepine**-2-carboxamide (hereinafter referred to as compound A) (0.55 g) and **lactic acid**-glycolic acid copolymer (**lactic acid** /glycolic acid=85/15 mole %, viscosity 0.164, weight average molecular weight about 14900, Wako Pure Chemical Industries) (4.45 g) were dissolved in. . .

DETD . . . harvested microcapsules were suspended in a small amount of distilled water and the suspension was lyophilized to give microcapsules containing **lactic acid**-glycolic acid copolymer. The mean particle diameter was 35 .mu.m.

DETD Production of Apatite-coated Microcapsule Containing **Lactic Acid**-glycolic Acid Copolymer

DETD The Compound A (0.4 g) and **lactic acid**-glycolic acid copolymer (**lactic acid**/glycolic acid=75/25 mole %, viscosity 0.160, weight average molecular weight about 13900, Wako Pure Chemical Industries) (3.6 g) were dissolved in. . .

DETD . . . harvested microcapsules were suspended in a small amount of distilled water and the suspension was lyophilized to give microcapsules containing **lactic acid**-glycolic acid copolymer. The mean particle diameter was 38 .mu.m.
DETD Production of Hydroxyapatite-coated Microcapsule Containing **Lactic Acid**-glycolic Acid Copolymer and Compound A
DETD Production of Hydroxyapatite-coated Microcapsule Containing **Lactic Acid**-glycolic Acid Copolymer and Gentamicin
DETD Production of Hydroxyapatite-coated Microcapsule Containing **Lactic Acid**-glycolic Acid Copolymer and Taxol
DETD Production of Hydroxyapatite-coated Microcapsule Containing **Lactic Acid**-glycolic Acid Copolymer and Indomethacin

L1 ANSWER 6 OF 15 USPATFULL
AN 2001:25462 USPATFULL
TI Pharmaceutical composition containing osteogenesis-promoting substance
IN Hoshino, Tetsuo, Toyono-gun, Japan
Saito, Kazuhiro, Amagasaki, Japan
Iwasa, Susumu, Kyotanabe, Japan
PA Takeda Chemical Industries, Ltd., Osaka, Japan (non-U.S. corporation)
PI US 6190695 B1 20010220
AI US 1999-246851 19990209 (9)
RLI Continuation of Ser. No. WO 1997-JP2941, filed on 25 Aug 1997
PRAI JP 1919-90408 19190409
JP 1996-223443 19960826
DT Utility
FS Granted
EXNAM Primary Examiner: Criares, T. J.
LREP Foley & Lardner
CLMN Number of Claims: 30
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1136
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention provides a pharmaceutical composition comprising a non-peptide osteogenesis-promoting substance and a polyethylene glycol or a derivative thereof, which can be advantageously used as a agent for preventing or treating various bone diseases (e.g., osteoporosis) in view of the high oral absorbability and stability of the active ingredient.
SUMM . . . implant comprising bone morphogenic protein (BMP) and polyethylene glycol 200 or 600 or a block polymer of polyethylene glycol and **lactic acid** is described.
SUMM (13) the pharmaceutical composition according to term (1), wherein the non-peptide osteogenesis-promoting substance is (2R,4S)-(-)-N-[4-(diethoxyphosphorylmethyl)phenyl]-1,2,4,5-tetrahydro-4-methyl-7,8-methylenedioxy-5-oxo-3-**benzothiepine**-2-carboxamide,
SUMM (15) the pharmaceutical composition according to term (14), which comprises (2R,4S)-(-)-N-[4-(diethoxyphosphorylmethyl)phenyl]-1,2,4,5-tetrahydro-4-methyl-7,8-methylenedioxy-5-oxo-3-**benzothiepine**-2-carboxamide and a polyethylene glycol,
SUMM (16) the pharmaceutical composition according to term (15), wherein the weight ratio of (2R,4S)-(-)-N-[4-diethoxyphosphorylmethyl)phenyl]-1,2,4,5-tetrahydro-4-methyl-7,8-methylenedioxy-5-oxo-3-**benzothiepine**-2-carboxamide relative to the pharmaceutical composition is about 0.05 to about 70% (w/w),
SUMM . . . invention is exemplified by the sulfur-containing heterocyclic compounds described in Japanese Patent Unexamined Publication Nos. 232880/1991, 364179/1992 and 294960/1993 (e.g., (2R,4S)-(-)-N-[4-(diethoxyphosphorylmethyl)phenyl]-1,2,4,5-tetrahydro-4-methyl-7,8-

methylenedioxy-5-oxo-3-**benzothiepine**-2-carboxamide) or salts thereof, the benzopyrane derivatives described in Japanese Patent Unexamined Publication No. 291983/1995 (e.g., N-(4-diethoxyphosphorylmethylphenyl)-4-oxo-4H-1-benzopyrane-2-carboxamide) or salts thereof, the. . .

SUMM A more preferable example of compound (I) is an optically active **benzothiepine** derivative represented by formula (II): ##STR10##

SUMM Preferable examples of compound (II) include, for example, (2R,4S)-(-)-N-[4-(diethoxyphosphorylmethyl)phenyl]-1,2,4,5-tetrahydro-4-methyl-7,8-methylenedioxy-5-oxo-3-**benzothiepine**-2-carboxamide (hereinafter also referred to as compound A) or a salt thereof.

CLM What is claimed is:

10. The pharmaceutical composition according to claim 1, wherein the non-peptide osteogenesis-promoting substance is (2R,4S)-(-)-N-[4-(diethoxyphosphorylmethyl)phenyl]-1,2,4,5-tetrahydro-4-methyl-7,8-methylenedioxy-5-oxo-3-**benzothiepine**-2-carboxamide.

11. The pharmaceutical composition according to claim 8, which comprises (2R,4S)-(-)-N-[4-(diethoxyphosphorylmethyl)phenyl]-1,2,4,5-tetrahydro-4-methyl-7,8-methylenedioxy-5-oxo-3-**benzothiepine**-2-carboxamide and a polyethylene glycol.

12. The pharmaceutical composition according to claim 11, wherein the weight ratio of (2R,4S)-(-)-N-[4-diethoxyphosphorylmethyl)phenyl]-1,2,4,5-tetrahydro-4-methyl-7,8-methylenedioxy-5-oxo-3-**benzothiepine**-2-carboxamide relative to the pharmaceutical composition is about 0.05 to about 70% (w/w).

L1 ANSWER 7 OF 15 USPATFULL
AN 2001:21788 USPATFULL
TI Stabilized pharmaceutical preparation
IN Fukuta, Makoto, Nara, Japan
Itoh, Hiroki, Suita, Japan
PA Takeda Chemical Industries, Ltd., Osaka, Japan (non-U.S. corporation)
PI US 6187340 B1 20010213
AI US 1998-149122 19980909 (9)
PRAI JP 1997-245778 19970910
DT Utility
FS Granted
EXNAM Primary Examiner: Williamson, Michael A.
LREP Wenderoth, Lind & Ponack, L.L.P.
CLMN Number of Claims: 19
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1140
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A stabilized pharmaceutical preparation which is coated with a coating agent comprising an agent for the protection from light, said agent being capable of producing free radicals when exposed to ultraviolet rays, and a free radical scavenger; which is stable to light, especially ultraviolet rays, or heat, and which has excellent storage-stability.

SUMM . . . saccharated pepsin, scopolia extract, cellulase AP3, lipase AP, cinnamon oil, etc.; intestinal function controlling drugs such as perperine hydrochloride, resistant **lactic acid** bacterium, Lactobacillus bifidus, etc.

SUMM preferably includes 2,3-dihydro[b]thiophene, 1,3-dihydrobenzo[c]thiophene, 3,4-dihydro-2H-1-benzothiopyran, 3,4-dihydro-1H-2-benzothiopyran, 2,3,4,5-tetrahydro-1-**benzothiepine**, 1,3,4,5-tetrahydro-2-**benzothiepine**,

1,2,4,5-tetrahydro-3-**benzothiepine**, 3,4,5,6-tetrahydro-2H-1-benzothiocine, 3,4,5,6-tetrahydro-1H-2-benzothiocine, 1,4,5,6-tetrahydro-2H-3-benzothiocine, 2,3,4,5,6,7-hexahydro-1-benzothionine, 1,3,4,5,6,7-hexahydro-2-benzothionine, 1,2,4,5,6,7-hexahydro-3-benzothionine, and 1,2,3,5,6,7-hexahydro-4-benzothionine, etc.

L1 ANSWER 8 OF 15 USPATFULL
AN 2000:117324 USPATFULL
TI Sustained-release preparation capable of releasing a physiologically active substance
IN Okada, Hiroaki, Osaka, Japan
Douken, Yayoi, Osaka, Japan
PA Takeda Chemical Industries, Ltd., Osaka, Japan (non-U.S. corporation)
PI US 6113943 20000905
AI US 1997-962347 19971031 (8)
PRAI JP 1996-290441 19961031
DT Utility
FS Granted
EXNAM Primary Examiner: Page, Thurman K.; Assistant Examiner: Seidleck, Brian K.
LREP Wenderoth, Lind & Ponack, L.L.P.
CLMN Number of Claims: 18
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1326
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Disclosed is a sustained-release preparation comprising 1) a polymer of **lactic acid** having a weight-average molecular weight of about 25,000 to about 60,000 and 2) a physiologically active substance, and which releases the physiologically active substance over a period of at least about 5 months; the sustained-release preparation shows an almost continuous zero order release of the physiologically active substance over a period of as long as about 5 months.
AB Disclosed is a sustained-release preparation comprising 1) a polymer of **lactic acid** having a weight-average molecular weight of about 25,000 to about 60,000 and 2) a physiologically active substance, and which releases. . .
SUMM . . . release of a polypeptide over a period of at least 2 months and containing a copolymer or homopolymer having a **lactic acid**/glycolic acid ratio of 80/20 to 100/0 and having a weight-average molecular weight of 7,000 to 30,000 are described.
SUMM (1) sustained-release preparation comprising 1) a polymer of **lactic acid** having a weight-average molecular weight of about 25,000 to about 60,000 and 2) a physiologically active substance, and which releases. . .
SUMM (2) the preparation according to the above (1), wherein the polymer of **lactic acid** is obtained by hydrolyzing a polylactic acid produced by ring-opening polymerization;
SUMM (3) the preparation according to the above (1), wherein the polymer of **lactic acid** is substantially free from a catalyst;
SUMM (4) the preparation according to the above (1), wherein the polymer of **lactic acid** has a weight-average molecular weight of about 30,000 to about 50,000;
SUMM (5) the preparation according to the above (1), wherein the polymer of **lactic acid** has a dispersity of about 1.2 to about 4.0;
SUMM . . . the preparation according to the above (1), wherein the ratio of the physiologically active substance relative to the polymer of **lactic acid** is about 0.01 to about 50% (w/w);

SUMM (15) the preparation according to the above (1), wherein the physiologically active substance is leuprorelin acetate, the polymer of **lactic acid** has a weight-average molecular weight of about 28,400 to about 47,800, and the preparation releases leuprorelin acetate over a period. . .

SUMM . . . a solution containing a physiologically active substance as an internal aqueous phase and with a solution containing a polymer of **lactic acid** having a weight-average molecular weight of about 25,000 to about 60,000 as an oil phase.

SUMM The polymer of **lactic acid** used in the present invention is a biodegradable polymer which decomposes in a living body over a period of at least about 5 months and has a free terminal carboxyl group. The present polymer is a homopolymer of **lactic acid**.

SUMM The weight-average molecular weight of the present polymer of **lactic acid** is about 25,000 to about 60,000, preferably about 27,000 to about 55,000, more preferably about 28,000 to about 50,000. Employment. . .

SUMM The dispersity (weight-average molecular weight/number-average molecular weight) of the polymer of **lactic acid** used in the present invention is preferably about 1.2 to about 4.0, more preferably about 1.5 to about 3.5.

SUMM The present polymer of **lactic acid** may be of the L-, D- or DL-configuration, with preference given to the DL-configuration. Regarding the DL-configuration, the ratio of. . .

SUMM The polymer of **lactic acid** used in the present invention is preferably produced by hydrolyzing a starting polylactic acid produced by ring-opening reaction of a cyclic dimer of **lactic acid** and polymerization.

SUMM . . . and polymerization is a polymer of a high molecular weight region, which is not obtained by a dehydration condensation of **lactic acid** wherein heating is conducted under reduced pressure after addition of a catalyst (JP-A 45920/1981, EP-A 26599), or a method for producing a polymer which is obtained by polymerization of **lactic acid** without using a catalyst and is substantially free from a catalyst (JP-A 28521/1986, EP-A 172636). The ring-opening reaction and polymerization (hereafter referred to as ring-opening polymerization) is conducted by a method wherein a cyclic dimer of a **lactic acid** is used and a catalyst is added while heating (e.g. J. H. R. Woodland et. al.; J. Med. Chem., 16,. . .

SUMM . . . polymerization is not especially limited as long as it is larger than the weight-average molecular weight of a polymer of **lactic acid** which is obtained by hydrolysis (about 25,000 to about 60,000), it ranges, for instance, from about 50,000 to about 200,000,. . .

SUMM Hydrolysis of a polylactic acid produced by ring-opening polymerization to obtain a polymer of **lactic acid** used in the present invention is conducted in the presence of an acid or a base according to a per. . .

SUMM . . . acid include inorganic acids such as hydrochloric acid, nitric acid, sulfuric acid and phosphoric acid; and organic acids such as **lactic acid**, acetic acid, tartaric acid, citric acid and succinic acid. Examples of the base include alkali metal hydroxides such as sodium. . .

SUMM . . . and the like. Therefore, it is appropriately decided by collecting a part of a polylactic acid and a polymer of **lactic acid** in the hydrolysis process and determining the weight-average molecular weight of the collected polylactic acid and a polymer of **lactic acid**. Duration of hydrolysis is

not especially limited but ranges, for instance, from about 1 hour to about 10 days, preferably. . .

SUMM . . . polymerization provides a sustained-release preparation with a large initial burst, the polylactic acid which is hydrolyzed, i.e. the polymer of **lactic acid** used in the present invention provides a sustained-release preparation with a small initial burst.

SUMM . . . solution into water or a mixed solution of water and a water-soluble organic solvent, and separating a precipitated polymer of **lactic acid**.

SUMM . . . water-soluble low-molecular compounds, for instance, those having the weight-average molecular weight of at most 1,000. Use of a polymer of **lactic acid** which is subjected to such refining process enables increasing an entrapment ratio of a physiologically active substance in a production. . .

SUMM Further, by hydrolyzing and refining a polylactic acid produced by ring-opening polymerization, a polymer of **lactic acid** is produced which is substantially free from a poisonous catalyst which is used in the ring-opening polymerization and exemplified by. . .

SUMM Examples of the osteogenesis promoters include polypeptides such as BMP, PTH, TGF-.beta. and IGF-1, and (2R,4S)-(-)-N-[4-(diethoxyphosphorylmethyl)phenyl]-1,2,4,5-tetrahydro-4-methyl-7,8-methylenedioxy-5-oxo-3-**benzothiepine**-2-carboxamide, 2-(3-pyridyl)-ethane-1,1-diphosphonic acid and raloxifene.

SUMM . . . not limited as long as it contains fine particles (i.e., microspheres) comprising a physiologically active substance and a polymer of **lactic acid**.

SUMM . . . small particles in which a physiologically active substance in a molecular form is dissolved or dispersed in a polymer of **lactic acid** as a solid solution, etc.

SUMM . . . preparation of the present invention include a sustained-release preparation, wherein the physiologically active substance is leuprorelin acetate, the polymer of **lactic acid** has a weight-average molecular weight of about 28,400 to about 47,800, and the preparation releases leuprorelin acetate over a period. . .

SUMM . . . a solution containing a physiologically active substance as an internal aqueous phase and with a solution containing a polymer of **lactic acid** as an oil phase. The microencapsulation is conducted by an in-water drying method, a phase separation method, a spray drying. . .

SUMM . . . a solution containing a physiologically active substance as an internal aqueous phase and with a solution containing a polymer of **lactic acid** of the present invention as an oil phase is produced, for example, as described below.

SUMM An internal aqueous phase thus obtained and a solution (oil phase) containing a polymer of **lactic acid** are mixed to obtain a mixture, which is then subjected to emulsification to yield a w/o emulsion.

SUMM As the solution (oil phase) containing a polymer of **lactic acid**, a solution may be employed that is prepared by dissolving the polymer of **lactic acid** in an organic solvent. Any organic solvent serves this purpose, as long as it has a boiling point not higher than about 120.degree. C., is hydrophobic and dissolves a polymer of **lactic acid**. Examples of such organic solvent include halogenated hydrocarbons (e.g., dichloromethane, chloroform, chloroethane, dichloroethane, trichloroethane, carbon tetrachloride), fatty acid esters (e.g.,. . .

SUMM Although varying depending on the kind and molecular weight of the polymer of **lactic acid** and the kind of organic solvent used, the polymer concentration in the organic solvent solution

is normally about 0.01 to. . .

SUMM . . . obtained is normally used after sterilizing or dust-cleaning filtration with a filter. Although depending on stability of a polymer of **lactic acid**, a solution containing a polymer of **lactic acid** may be stored in a closed container at room temperature or in a cold place.

SUMM . . . mixing ratio of an aqueous solution containing a physiologically active substance and an organic solvent solution containing a polymer of **lactic acid** is normally about 0.1 to about 1000 parts by weight, preferably about 1 to about 100 parts by weight of. . . used, desired pharmacological action, duration of action and other factors, the ratio of the physiologically active substance to polymer of **lactic acid** is normally about 0.01 to about 50% (w/w), preferably about 0.5 to about 40% (w/w), and especially preferably about 0.1. . .

SUMM . . . internal aqueous phase is finer beyond a certain extent, an interaction between a physiologically active substance and a polymer of **lactic acid** becomes stronger and a release control by a polymer of **lactic acid** depends on biodegradability of the polymer of **lactic acid** to make a long-term release control more accurate, which is preferable.

SUMM . . . agent is gradually added to a w/o emulsion while the emulsion is stirred, to precipitate and solidify a polymer of **lactic acid**. Any coacervating agent can be used, as long as it is a polymeric, mineral oil or vegetable oil compound miscible with the solvent for a polymer of **lactic acid** and that does not dissolve a polymer of **lactic acid** for capsulation. Examples of such coacervating agents include silicon oil, sesame oil, soybean oil, corn oil, cotton seed oil, coconut. . .

DETD . . . Boehringer Ingelheim, Germany)(hereafter referred to as Polymer F) was hydrolyzed by soaking it in 400 ml of a solution wherein DL-**lactic acid** was diluted with distilled water 1/50 or 1/100 (w/w) times (respectively pH 2.09, pH 2.27) at 60.degree. C.

DETD . . . dried for one day at 40.degree. C. under reduced pressure. Before the organic solvent phase were solidified completely, polymer of **lactic acid** was foamed by adjusting the degree of vacuum to enlarge the volume of the polymer of **lactic acid** and then promote evaporation of dichloromethane. The foamed substance obtained was pulverized to yield polymers shown in Table 1.

DETD TABLE 1

Lactic acid conc. (w/w)	Hydrolyzation time (day)	Weight-average molecular weight	Yield (%)	Polymer
1/50	2	47,800	96.6	A
1/100	3	31,200	82.7	B
1/50	3. . .			

DETD TABLE 2

Lactic acid conc. (w/w)	Hydrolyzation time (day)	Weight-average molecular weight	Yield

			(%) Polymer	
1/50	1.1	69,200	59.3	D
1/50	1.2	62,300	--	E

CLM What is claimed is:

1. A sustained-release preparation comprising 1) a hydrolyzed polymer of **lactic acid** having a weight-average molecular weight of about 25,000 to about 60,000 and a dispersity of about 1.2 to about 4.0. . .

2. The preparation according to claim 1, wherein the hydrolyzed polymer of **lactic acid** is obtained by hydrolyzing a polylactic acid produced by ring-opening polymerization.

3. The preparation according to claim 1, wherein the hydrolyzed polymer of **lactic acid** is substantially free from a catalyst.

4. The preparation according to claim 1, wherein the hydrolyzed polymer of **lactic acid** has a weight-average molecular weight of about 30,000 to about 50,000.

. . . 13. The preparation according to claim 1, wherein the ratio of the physiologically active substance relative to the polymer of **lactic acid** is about 0.01 to about 50% (w/w).

14. The preparation according to claim 1, wherein the physiologically active substance is leuprorelin acetate, the hydrolyzed polymer of **lactic acid** has a weight-average molecular weight of about 28,400 to about 47,800, and the preparation releases leuprorelin acetate over a period. . .

. . . solution containing a physiologically active substance as an internal aqueous phase and with a solution containing a hydrolyzed polymer of **lactic acid** having a weight-average molecular weight of about 25,000 to about 60,000 and a dispersity of about 1.2 to about 4.0. . .

. . . solution into water or a mixed solution of water and a water-soluble organic solvent, and separating a precipitated polymer of **lactic acid**.

L1 ANSWER 9 OF 15 USPATFULL
AN 2000:31050 USPATFULL
TI Sustained release microspheres and preparation thereof
IN Takechi, Nobuyuki, Osaka, Japan
Ohtani, Seiji, Osaka, Japan
Nagai, Akihiro, Osaka, Japan
PA Takeda Chemical Industries, Ltd., Osaka, Japan (non-U.S. corporation)
PI US 6036976 20000314
AI US 1998-154164 19980916 (9)
RLI Division of Ser. No. US 1996-766611, filed on 13 Dec 1996, now patented, Pat. No. US 5851451
DT Utility
FS Granted
EXNAM Primary Examiner: Page, Thurman K.; Assistant Examiner: Channavajjala, Lakshmi
LREP Wenderoth, Lind & Ponack, L.L.P.
CLMN Number of Claims: 15
ECL Exemplary Claim: 1
DRWN No Drawings

LN.CNT 1144
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disclosed is a method of producing microspheres which comprises subjecting a w/o/w emulsion or o/w emulsion to an in-water drying method under the following conditions:

1) the amount of microspheres per m.sup.3 of an external aqueous phase is about 0.1 to about 500 kg,

2) the square root of the area (unit: m.sup.2) of the liquid surface in contact with the gas phase is about 0.2 to about 4.5 per the cube root of the volume (unit: m.sup.3) of an external aqueous phase,

3) the w/o/w emulsion or o/w emulsion is replaced at the replacement frequency of about 0.01 to about 10 times/minutes,

4) a gas is blown to the w/o/w emulsion or o/w emulsion at the gas transfer rate near the liquid surface of about 0.1 to about 300 m/second, and

5) the gas is replaced at the replacement frequency of not less than about 0.5 times/minutes;

and the method of the present invention increases the rate of solvent removal from microspheres in in-water drying, reduces the amount of solvent in microspheres in a short time.

SUMM Examples of the osteogenesis promoters include polypeptides such as BMP, PTH, TGF-.beta. and IGF-1, and (2R,4S)-(-)-N-[4-(diethoxyphosphorylmethyl)phenyl]-1,2,4,5-tetrahydro-4-methyl-7,8-methylenedioxy-5-oxo-3-**benzothiepine**-2-carboxamide and 2-(3-pyridyl)-ethane-1,1-diphosphonic acid,

SUMM . . . having a free terminal carboxyl group include homopolymers and copolymers synthesized from one or more .alpha.-hydroxy acids (e.g., glycolic acid, **lactic acid**, hydroxybutyric acid), hydroxydicarboxylic acids (e.g., malic acid), hydroxytricarboxylic acids (e.g., citric acid) etc. by catalyst-free dehydration condensation polymerization, mixtures thereof,. . .

SUMM The biodegradable polymer having a free terminal carboxyl group is preferably (1) a **lactic acid**/glycolic acid polymer (including homopolymers such as polylactic acid and polyglycolic acid, and copolymer of **lactic acid** and glycolic acid) or (2) a biodegradable polymer consisting of a mixture of (A) a copolymer of a glycolic acid. . .

SUMM When the biodegradable polymer used is a **lactic acid**/glycolic acid polymer, its composition ratio (**lactic acid**/glycolic acid) (mol %) is preferably about 100/0 to about 40/60, more preferably about 90/10 to about 50/50.

SUMM The weight-average molecular weight of the above-described **lactic acid**/glycolic acid polymer is preferably about 5,000 to about 25,000, more preferably about 7,000 to about 20,000.

SUMM The degree of dispersion (weight-average molecular weight/number-average molecular weight) of the **lactic acid**/glycolic acid polymer is preferably about 1.2 to about 4.0, more preferably about 1.5 to about 3.5.

SUMM The above-described **lactic acid**/glycolic acid polymer can be produced by a known process, such as that described in Japanese Patent Unexamined Publication No. 28521/1986.

SUMM The decomposition/elimination rate of a **lactic acid**/glycolic acid polymer varies widely, depending on composition or molecular weight. Drug release duration can be extended by lowering the

glycolic. . . or decreasing the molecular weight. To obtain a long-term (e.g., 1-4 months) sustained-release preparation, it is preferable to use a **lactic acid**/glycolic acid polymer whose composition ratio and weight-average molecular weight fall in the above-described ranges. With a **lactic acid**/glycolic acid polymer that decomposes more rapidly than that whose composition ratio and weight-average molecular weight fall in the above ranges, initial burst is difficult to suppress. On the contrary, with a **lactic acid**/glycolic acid polymer that decomposes more slowly than that whose composition ratio and weight-average molecular weight fall in the above ranges,. . .

SUMM For producing a polylactic acid, two methods are known: ring-opening polymerization of lactide, a dimer of **lactic acid**, and dehydration condensation polymerization of **lactic acid**. For obtaining a polylactic acid of relatively low molecular weight for the present invention, direct dehydration condensation polymerization of **lactic acid** is preferred. Such a method, for example, can be carried out in accordance with the method described in Japanese Patent. . .

SUMM A biodegradable polymer having a free terminal carboxyl group is more preferably a **lactic acid**/glycolic acid polymer. Especially, a **lactic acid**/glycolic acid polymer having a composition ratio (**lactic acid**/glycolic acid) (mol %) of 100/0 is a polylactic acid. Microspheres produced by using a polylactic acid are able to release. . .

DETD . . . gelatin were weighed and completely dissolved in 66 ml of water for injection. To this solution, 521.9 g of a **lactic acid**/glycolic acid copolymer [**lactic acid**/glycolic acid=75/25 (mol %), weight-average molecular weight: about 11,000] dissolved in 873.6 g of dichloromethane (methylene chloride) was added, followed by. . .

DETD . . . solution of 0.5 g of thyrotropin-releasing hormone (TRH) in 0.2 g of water, a solution of 4.5 g of a **lactic acid**/glycolic acid copolymer [**lactic acid**/glycolic acid=75/25 (w/w), weight-average molecular weight; about 14000] in dichloromethane (4.9 ml) was added to yield a w/o emulsion.

DETD . . . gelatin were weighed and completely dissolved in 120 ml of water for injection. To this solution, 957.2 g of a **lactic acid**/glycolic acid copolymer [**lactic acid**/glycolic acid=75/25 (mol %), weight-average molecular weight: about 11,000] dissolved in 1602.8 g of dichloromethane was added, followed by stirring and. . .

DETD . . . gelatin were weighed and completely dissolved in 80 ml of water for injection. To this solution, 646.1 g of a **lactic acid**/glycolic acid copolymer [**lactic acid**/glycolic acid=75/25 (mol %), weight-average molecular weight: about 11,000] dissolved in 1081.9 g of dichloromethane was added, followed by stirring and. . .

CLM What is claimed is:

7. The microsphere according to claim 1, wherein the biodegradable polymer is a **lactic acid**/glycolic acid polymer.

10. The microsphere according to claim 7, wherein the composition ratio of a **lactic acid**/glycolic acid is from about 90/10 to about 50/50.

. . . than about 0.5 times/minute, wherein the physiologically active substance is leuprorelin or leuprorelin acetate, and the biodegradable polymer is a **lactic acid**/glycolic acid polymer having a composition ratio of about 90/10 to 50/50.

L1 ANSWER 10 OF 15 USPATFULL
AN 2000:15340 USPATFULL
TI Method for producing a microparticle
IN Takechi, Nobuyuki, Osaka, Japan
Nonomura, Muneo, Toyonaka, Japan
Higuchi, Shigehiro, Amagasaki, Japan
Beppu, Toshiharu, Nishinomiya, Japan
PA Takeda Chemical Industries, Ltd., Osaka, Japan (non-U.S. corporation)
PI US 6022564 20000208
AI US 1999-260797 19990301 (9)
RLI Continuation of Ser. No. WO 1997-JP3608, filed on 8 Oct 1997
PRAI JP 1996-268704 19961009
DT Utility
FS Granted
EXNAM Primary Examiner: Nutter, Nathan M.
LREP Riesen, Philippe Y.
CLMN Number of Claims: 15
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1194
AB This invention provides a method for producing a microparticle which comprises pulverizing a solid preparation comprising a compound represented by the formula: ##STR1## wherein ring A is an optionally substituted benzene ring; R is a hydrogen atom or an optionally substituted hydrocarbon group; B is an optionally esterified or amidated carboxyl group; X is --CH(OH)-- or --CO--; k is 0 or 1; and n is 0, 1 or 2 or a pharmaceutically acceptable salt thereof and a biodegradable polymer of .alpha.-hydroxycarboxylic acid in the presence of a pulverizing auxiliary, which can provide microparticles which are less adhesive and involve less aggregation and are thus excellent in drug entrapment ratio and control of drug-release in a desired particle size.
SUMM (5) a method according to above (1), wherein the .alpha.-hydroxycarboxylic acid is **lactic acid** and/or glycolic acid,
SUMM (19) a method for producing a microparticle of (2R,4S)-(-)-N-[4-(diethoxyphosphorylmethyl)phenyl]-1,2,4,5-tetrahydro-4-methyl-7,8-methylenedioxy-5-oxo-3-**benzothiepine**-2-carboxamide or a pharmaceutically acceptable salt thereof as an active ingredient which comprises pulverizing a solid dispersion comprising the active ingredient and a glycolic acid-**lactic acid** copolymer having a weight-average molecular weight in the range from about 3,000 to about 30,000 and the ratio of **lactic acid** /glycolic acid is about 60/40 to 100/0 in the presence of a pulverizing auxiliary with or without (1) a water-soluble polymer. . .
SUMM (20) a method for producing a microparticle of (2R,4S)-(-)-N-[4-(diethoxyphosphorylmethyl)phenyl]-1,2,4,5-tetrahydro-4-methyl-7,8-methylenedioxy-5-oxo-3-**benzothiepine**-2-carboxamide or a pharmaceutically acceptable salt thereof which comprises pulverizing a solid dispersion comprising the active ingredient and glycolic acid/**lactic acid** copolymer having a weight-average molecular weight in the range from about 3,000 to about 30,000 and the ratio of **lactic acid**/glycolic acid is about 60/40 to 100/0 in the presence of a pulverizing auxiliary with either (1) a water-soluble polymer or. . .
SUMM (21) a method for producing a microparticle of (2R,4S)-(-)-N-[4-(diethoxyphosphorylmethyl)phenyl]-1,2,4,5-tetrahydro-4-methyl-7,8-methylenedioxy-5-oxo-3-**benzothiepine**-2-carboxamide or a pharmaceutically acceptable salt thereof which comprises pulverizing a

solid dispersion comprising the active ingredient and glycolic acid/**lactic acid** copolymer having a weight-average molecular weight in the range from about 3,000 to about 30,000 and the ratio of **lactic acid**/glycolic acid is about 60/40 to 100/0 in the presence of a pulverizing auxiliary optionally followed by coating the resultant microparticle. . .

SUMM Most preferably, the compound (II) is, for example, (2R,4S)-(-)-N-[4-(diethoxyphosphorylmethyl)phenyl]-1,2,4,5-tetrahydro-4-methyl-7,8-methylenedioxy-5-oxo-3-**benzothiepine**-2-carboxamide (hereinafter also referred to as compound A).

SUMM . . . in Japanese laid-open patent applications 232880/1991 (corresponding to EP-A-0376197), 364179/1992 (corresponding to EP-A-0460488), 294960/1994, etc. or a salt thereof (e.g. (2R,4S)-(-)-N-(4-(diethoxyphosphorylmethyl)phenyl]-1,2,4,5-tetrahydro-4-methyl-7,8-methylendioxy-5-oxo-3-**benzothiepine**-2-carboxamide) and **benzothiepine** derivatives specifically disclosed in Japanese laid-open application 231569/1996 (corresponding to EP-A-0719782), These compounds may be used in a combination of. . .

SUMM The preferable embodiments of hydroxycarboxylic acid represented by the formula [III] is exemplified by glycolic acid, **lactic acid**, 2-hydroxybutyric acid, 2-hydroxyvaleric acid, 2-hydroxy-3-methylbutyric acid, 2-hydroxycaproic acid, 2-hydroxyisocaproic acid and 2-hydroxycapric acid, with preference given to glycolic acid, **lactic acid**, 2-hydroxy-butyric acid, 2-hydroxyvaleric acid, 2-hydroxy-3-methyl-butyric acid and 2-hydroxycaproic acid. When optical isomers of these .alpha.-hydroxycarboxylic acid exist, any one of. . .

SUMM The .alpha.-hydroxycarboxylic acid singly used for polymerization is preferably glycolic acid, **lactic acid**, 2-hydroxybutyric acid, more preferably **lactic acid**.

SUMM The preferable examples of the above-mentioned copolymers include copolymers of glycolic acid and **lactic acid** (glycolic acid/**lactic acid** copolymers) and copolymers of glycolic acid and a .alpha.-hydroxycarboxylic acid represented by the formula [III] wherein R.sup.6 is C.sub.2-8 alkyl group (e.g. ethyl, propyl, isopropyl, butyl, isobutyl, hexyl, 2,2-dimethylbutyl, 2-ethylbutyl, etc.) (hereinafter referred to as glycolic acid copolymer). Glycolic acid/**lactic acid** copolymers and copolymers of glycolic acid and 2-hydroxycarboxylic acid are more preferable.

SUMM With respect to the content ratio of **lactic acid** and glycolic acid of the **lactic acid**/glycolic acid copolymer, **lactic acid** preferably accounts for about 40 to about 95 mol % and glycolic acid preferably accounts for about 60 to about 5 mol %, more preferably **lactic acid** accounts for about 50 to about 95 mol % and glycolic acid accounts for about 50 to about 5 mol %, even more preferably **lactic acid** accounts for about 60 to about 90 mol % and glycolic acid accounts for about 40 to about 10 mol. . .

SUMM The weight-average molecular weight of the **lactic acid**/glycolic acid copolymer used in the present invention is preferably about 1,000 to about 100,000, more preferably about 2,000 to about. . .

SUMM The degree of dispersion of the **lactic acid**/glycolic acid copolymer (weight-average molecular weight/number-average molecular weight) is preferably about 1.2 to about 4.0, more preferably about 1.5 to about. . .

SUMM The glycolic acid/**lactic acid** copolymer and the glycolic acid copolymer above can be produced by known processes, such as that described in Japanese laid-open. . .

SUMM For example, when **benzothiepine** derivatives or a pharmaceutically acceptable salt thereof are administered to an adult subject in need (weighing 50 kg) in. . .

DETD In 160 grams of dichloromethane were dissolved 10.0 g of (2R,4S)-(-)-N-[4-(diethoxyphosphorylmethyl)phenyl]-1,2,4,5-tetrahydro-4-methyl-7,8-methylenedioxy-5-oxo-3-**benzothiepine**-2-carboxamide (prepared according to Japanese Patent Laid Open Publication No. Hei8-231569 (hereinafter, referred to as "Compound A") and 90 grams of dl-**lactic acid**/glycolic acid copolymer (hereinafter referrd to as "copoly (dl-lactic/glycolic acid)") The **lactic acid**/glycolic acid ratio (hereinafter simply abbreviated as (L/G))=85/15; Weight-average molecular weight: 14,000. The resultant solution was poured into a container coated. . .

CLM What is claimed is:
5. A method according to claim 1, wherein the .alpha.-hydroxycarboxylic acid is **lactic acid** and/or glycolic acid.

L1 ANSWER 11 OF 15 USPATFULL
AN 1999:65248 USPATFULL
TI Osteogenic promoting pharmaceutical composition
IN Hoshino, Tetsuo, Osaka, Japan
Muranishi, Hiroya, Kyoto, Japan
Taketomi, Shigehisa, Osaka, Japan
Iwasa, Susumu, Kyoto, Japan
PA Takeda Chemical Industries, Ltd., Osaka, Japan (non-U.S. corporation)
PI US 5910492 19990608
AI US 1996-719467 19960925 (8)
PRAI JP 1995-138036 19950605
JP 1996-11686 19960126
WO 1996-JP1506 19960604
DT Utility
FS Granted
EXNAM Primary Examiner: Criares, Theodore J.
LREP Foley & Lardner
CLMN Number of Claims: 16
ECL Exemplary Claim: 1
DRWN 3 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 1509
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention provides a pharmaceutical composition comprising a non-peptide osteogenic promoting substance and a biodegradable polymer, which can be safely used as a prophylactic/therapeutic agent for various bone diseases (e.g., bone fractures).

SUMM (15) a pharmaceutical composition according to (1), wherein the compound is (2R, 4S)-(-)-N-[4-(diethoxyphosphorylmethyl)phenyl]-1,2,4,5-tetrahydro-4-methyl-7,8-methylenedioxy-5-oxo-3-**benzothiepine**-2-carboxamide,

SUMM (17) a pharmaceutical composition according to (1), which comprises (2R,4S)-(-)-N-[4-(diethoxyphosphorylmethyl)phenyl]-1,2,4,5-tetrahydro-4-methyl-7,8-methylenedioxy-5-oxo-3-**benzothiepine**-2-carboxamide, a biodegradable polymer,

SUMM (20) a pharmaceutical composition according to (17), wherein the content ratio of (2R,4S)-(-)-N-[4-diethoxyphosphorylmethyl)phenyl]-1,2,4,5-tetrahydro-4-methyl-7,8-methylenedioxy-5-oxo-3-**benzothiepine**-2-carboxamide based on the biodegradable polymer is about 5 to 30% (w/w), and the content ratio of sodium phosphate based on (2R,4S)-(-)-[N-(diethoxyphosphorylmethyl)phenyl]-1,2,4,5-tetrahydro-4-methyl-7,8-methylenedioxy-5-oxo-3-**benzothiepine**-2-carboxamide and the biodegradable polymer is about 0.1 to 20% (w/w),

SUMM (21) a pharmaceutical composition according to (17), wherein the biodegradable polymer is a **lactic acid**-glycolic acid copolymer,

SUMM (24) a pharmaceutical composition according to (23), wherein the aliphatic polyester is a **lactic acid**-glycolic acid copolymer,

SUMM Useful non-peptide osteogenic promoting substances of the present invention include the sulfur-containing heterocyclic compounds such as (2R,4S)-(-)-N-[4-(Diethoxyphosphorylmethyl)phenyl]-1,2,4,5-tetrahydro-4-methyl-7,8-methylenedioxy-5-oxo-3-**benzothiepine**-2-carboxamide or salts thereof described in U.S. Pat. No. 5,071,841, U.S. Pat. No. 5,158,943 and JP5294960, the benzopyrane derivatives such as. . .

SUMM Most preferably, the compound (II) is, for example, (2R,4S)-(-)-N-[4-(diethoxyphosphorylmethyl)phenyl]-1,2,4,5-tetrahydro-4-methyl-7,8-methylenedioxy-5-oxo-3-**benzothiepine**-2-carboxamide (hereinafter also referred to as compound A).

SUMM . . . include fatty acid polyesters such as polymers, copolymers and their mixture of one or more kinds of .alpha.-hydroxycarboxylic acids (e.g., **lactic acid**, glycolic acid, 2-hydroxybutyric acid, 2-hydroxyvaleric acid, 2-hydroxy-3-methylbutyric acid, 2-hydroxycaproic acid, 2-hydroxyisocaproic acid, 2-hydroxycaprylic acid), hydroxydicarboxylic acids (e.g., malic acid) and hydroxytricarboxylic acids (e.g., malic acid), **lactic acid** caprolactones, valerolactones, etc., and derivatives thereof (e.g., block polymers of polylactic acid, polyglycolic acid and polyethylene glycol), poly-.alpha.-cyanoacrylates, poly-.beta.-hydroxybutyric acid,. . .

SUMM . . . copolymers synthesized from one or more kinds of .alpha.-hydroxycarboxylic acids-are preferred. Specifically, copolymers synthesized from one or more kinds of **lactic acid**, glycolic acid, 2-hydroxybutyric acid, 2-hydroxyvaleric acid etc., or mixtures thereof are used.

SUMM Homopolymers of the above-mentioned .alpha.-hydroxycarboxylic acids include homopolymers of **lactic acid**, glycolic acid and 2-hydroxybutyric acid. The preferable .alpha.-hydroxycarboxylic acid is **lactic acid**. Copolymers of the above-mentioned .alpha.-hydroxycarboxylic acids include copolymers of glycolic acid and the other .alpha.-hydroxycarboxylic acids. Preferable .alpha.-hydroxycarboxylic acids are **lactic acid** and 2-hydroxybutyric acid. Specifically, useful copolymers include **lactic acid**-glycolic acid copolymers and 2-hydroxybutyric acid-glycolic acid copolymers, with preference given to **lactic acid**-glycolic acid copolymers, etc.

SUMM The weight-average molecular weight of a **lactic acid** homopolymer (hereinafter also referred to as polylactic acid) is preferably about 5,000 to 100,000, more preferably about 6,000 to 50,000.. . .

SUMM The content ratio of **lactic acid** and glycolic acid in a **lactic acid**-glycolic acid copolymer is preferably about 100/0 to 50/50 (w/w), and more preferably about 90/10 to 50/50 (w/w). The weight-average molecular weight of the **lactic acid**-glycolic acid copolymer is preferably about 5,000 to 100,000, more preferably about 8,000 to 50,000. The **lactic acid**-glycolic acid copolymer can be synthesized by a commonly known production method such as that described in EP172636. The copolymer is. . .

SUMM (A) a **lactic acid**-glycolic acid copolymer:

SUMM wherein the ratio of **lactic acid**/glycolic acid is about 90/10 to 50/50 (w/w) and the weight-average molecular weight is about 8000 to 50000,

SUMM (B) (2R,4S)-(-)-N-[4-(diethoxyphosphorylmethyl)phenyl]-1,2,4,5-tetrahydro-4-methyl-7,8-methylenedioxy-5-oxo-3-**benzothiepine**-2-carboxamide, and

DETD Production of (2R,4S)-(-)-1,2,4,5-tetrahydro-4-methyl-7,8-methylenedioxy-5-oxo-3-**benzothiepine**-2-carboxylic acid (R)-.alpha.-methoxycarbonylbenzyl ester

DETD A solution of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (12.59 g) in dichloromethane (200 ml) was added drop by drop to a solution of (.+-.)-t-1,2,4,5-tetrahydro-4-methyl-7,8-methylenedioxy-5-oxo-3-**benzothiepine**-2-carboxylic acid (15.34 g) and methyl (R)-(-)-mandelic acid (18.19 g) in N,N-dimethylformamide (DMF) (200 ml) at 0.degree. C., followed by the. . .

DETD Production of (2R,4S)-(-)-1,2,4,5-tetrahydro-4-methyl-7,8-methylenedioxy-5-oxo-3-**benzothiepine**-2-carboxylic acid

DETD A mixture of (2R,4S)-(-)-1,2,4,5-tetrahydro-4-methyl-7,8-methylenedioxy-5-oxo-3-**benzothiepine**-2-carboxylic acid (R)-.alpha.-methoxycarbonylbenzyl ester as obtained in Reference Example 1 (4.18 g), acetic acid (45 ml) and concentrate hydrochloric acid (30. . .

DETD Production of (2R,4S)-(-)-N-[4-(diethoxyphosphorylmethyl)phenyl]-1,2,4,5-tetrahydro-4-methyl-7,8-methylenedioxy-5-oxo-3-**benzothiepine**-2-carboxamide (compound A) ##STR12##

DETD A solution of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.39 g) in dichloromethane (7 ml) was added drop by drop to a solution of (2R,4S)-(-)-1,2,4,5-tetrahydro-4-methyl-7,8-methylenedioxy-5-oxo-3-**benzothiepine**-2-carboxylic acid (0.47 g) as obtained in Reference Example 2 (0.41 g) and diethyl 4-aminobenzylphosphonate (0.41 g) in N,N-dimethylformamide (DMF) (7. . .

DETD A dichloromethane solution of a **lactic acid**-glycolic acid copolymer "hereinafter also referred to as PLGA; **lactic acid**-glycolic acid content ratio (mol %) and weight-average molecular weight based on GPC measurement are shown in Table 1; produced by Wako Pure Chemical Industry" and a **lactic acid** homopolymer (hereinafter also referred to as PLA) was prepared (hereinafter also referred to as solution A), using a formula shown. . .

DETD . . . 5

PLGA 90/10 20000	2.4	2.0	0.1	1.0	400	65
No. 6 PLGA 85/15 12100	2.4	2.0	0.1	1.0	800	51

*__Lactic acid__/Glycolic acid Content Ratio

DETD About 8 g of a **lactic acid**-valerolactone copolymer (PLV 2500ML, produced by Taki Chemical, hereinafter also referred to as PLV) or a glycolic acid-caprolactone copolymer (PGC 2500MG,. . .

DETD . . . compound A (content ratio 10%) was prepared in the same manner as in Example 1, except that PLGA having a **lactic acid**-glycolic acid content ratio of 85/15 (mol %) and weight-average molecular weight of 14,900 (produced by Wako Pure Chemical Industry). Mean. . .

DETD A dichloromethane solution containing 2.4 g of PLGA (produced by Wako Pure Chemical Industry) whose the **lactic acid**/glycolic acid content ratio is 85/15 and the weight-average molecular weight is 14,900 and 0.1 g of the compound A was. . .

CLM What is claimed is:

. . . comprising a sustained-release microcapsule having a release time of from 1 week to 3 months comprising a composition comprising (2R,4S)-(-)-N-[4-(diethoxyphosphorylmethyl) phenyl]-1,2,4,5-tetrahydro-4-methyl-7,8-methylenedioxy-5-oxo-3-**benzothiepine**-2-carboxamide and a biodegradable polymer.

8. A pharmaceutical composition according to claim 1, wherein the content ratio of (2R,4S)-(-)-N-[4-diethoxyphosphorylmethyl)phenyl]-1,2,4,5-tetrahydro-4-methyl-7,8-methylenedioxy-5-oxo-3-**benzothiepine**-2-carboxamide based on the biodegradable polymer is about 5 to 30% (w/w), and the content ratio of sodium phosphate based on (2R,4S)-(-)-[N-(diethoxyphosphorylmethyl)phenyl]-1,2,4,5-tetrahydro-4-methyl-7,8-methylenedioxy-5-oxo-3-**benzothiepine**-2-carboxamide and the biodegradable polymer is about 0.1 to 20% (w/w).

9. A pharmaceutical composition according to claim 1, wherein the biodegradable polymer is a **lactic acid**-glycolic acid copolymer.

12. A pharmaceutical composition according to claim 11, wherein the aliphatic polyester is a **lactic acid**-glycolic acid copolymer.

L1 ANSWER 12 OF 15 USPATFULL
AN 1998:159393 USPATFULL
TI Production of microspheres
IN Takechi, Nobuyuki, Osaka, Japan
Ohtani, Seiji, Osaka, Japan
Nagai, Akihiro, Osaka, Japan
PA Takeda Chemical Industries, Ltd., Osaka, Japan (non-U.S. corporation)
PI US 5851451 19981222
AI US 1996-766611 19961213 (8)
PRAI JP 1995-327690 19951215
DT Utility
FS Granted
EXNAM Primary Examiner: Nutter, Nathan M.
LREP Wenderoth, Lind & Ponack,LLP
CLMN Number of Claims: 14
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1150
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Disclosed is a method of producing microspheres which comprises subjecting a w/o/w emulsion or o/w emulsion to an in-water drying method under the following conditions:

1) the amount of microspheres per m.sup.3 of an external aqueous phase is about 0.1 to about 500 kg,

2) the square root of the area (unit: m.sup.2) of the liquid surface in contact with the gas phase is about 0.2 to about 4.5 per the cube root of the volume (unit: m.sup.3) of an external aqueous phase,

3) the w/o/w emulsion or o/w emulsion is replaced at the replacement frequency of about 0.01 to about 10 times/minutes,

4) a gas is blown to the w/o/w emulsion or o/w emulsion at the gas transfer rate near the liquid surface of about 0.1 to about 300

m/second, and

5) the gas is replaced at the replacement frequency of not less than about 0.5 times/minutes;

and the method of the present invention increases the rate of solvent removal from microspheres in in-water drying, reduces the amount of solvent in microspheres in a short time.

SUMM Examples of the osteogenesis promoters include polypeptides such as BMP, PTH, TGF-.beta. and IGF-1, and (2R,4S)-(-)-N-[4-(diethoxyphosphorylmethyl)phenyl]-1,2,4,5-tetrahydro-4-methyl-7,8-methylenedioxy-5-oxo-3-**benzothiepine**-2-carboxamide and 2-(3-pyridyl)-ethane-1,1-diphosphonic acid.

SUMM . . . having a free terminal carboxyl group include homopolymers and copolymers synthesized from one or more .alpha.-hydroxy acids (e.g., glycolic acid, **lactic acid**, hydroxybutyric acid), hydroxydicarboxylic acids (e.g., malic acid), hydroxytricarboxylic acids (e.g., citric acid) etc. by catalyst-free dehydration condensation polymerization, mixtures thereof,. . .

SUMM The biodegradable polymer having a free terminal carboxyl group is preferably (1) a **lactic acid**/glycolic acid polymer (including homopolymers such as polylactic acid and polyglycolic acid, and copolymer of **lactic acid** and glycolic acid) or (2) a biodegradable polymer consisting of a mixture of (A) a copolymer of a glycolic acid. . .

SUMM When the biodegradable polymer used is a **lactic acid**/glycolic acid polymer, its composition ratio (**lactic acid**/glycolic acid) (mol %) is preferably about 100/0 to about 40/60, more preferably about 90/10 to about 50/50.

SUMM The weight-average molecular weight of the above-described **lactic acid**/glycolic acid polymer is preferably about 5,000 to about 25,000, more preferably about 7,000 to about 20,000.

SUMM The degree of dispersion (weight-average molecular weight/number-average molecular weight) of the **lactic acid**/glycolic acid polymer is preferably about 1.2 to about 4.0, more preferably about 1.5 to about 3.5.

SUMM The above-described **lactic acid**/glycolic acid polymer can be produced by a known process, such as that described in Japanese Patent Unexamined Publication No. 28521/1986.

SUMM The decomposition/elimination rate of a **lactic acid**/glycolic acid polymer varies widely, depending on composition or molecular weight. Drug release duration can be extended by lowering the glycolic. . . or decreasing the molecular weight. To obtain a long-term (e.g., 1-4 months) sustained-release preparation, it is preferable to use a **lactic acid**/glycolic acid polymer whose composition ratio and weight-average molecular weight fall in the above-described ranges. With a **lactic acid**/glycolic acid polymer that decomposes more rapidly than that whose composition ratio and weight-average molecular weight fall in the above ranges, initial burst is difficult to suppress. On the contrary, with a **lactic acid**/glycolic acid polymer that decomposes more slowly than that whose composition ratio and weight-average molecular weight fall in the above ranges,. . .

SUMM For producing a polylactic acid, two methods are known: ring-opening polymerization of lactide, a dimer of **lactic acid**, and dehydration condensation polymerization of **lactic acid**. For obtaining a polylactic acid of relatively low molecular weight for the present invention, direct dehydration condensation polymerization of **lactic acid** is preferred. Such a method, for example, can be carried out in accordance

with the method described in Japanese Patent. . .

SUMM A biodegradable polymer having a free terminal carboxyl group is more preferably a **lactic acid**/glycolic acid polymer. Especially, a **lactic acid**/glycolic acid polymer having a composition ratio (**lactic acid**/glycolic acid) (mol %) of 100/0 is a polylactic acid. Microspheres produced by using a polylactic acid are able to release. . .

DETD . . . gelatin were weighed and completely dissolved in 66 ml of water for injection. To this solution, 521.9 g of a **lactic acid**/glycolic acid copolymer [**lactic acid** /glycolic acid=75/25 (mol %), weight-average molecular weight: about 11,000] dissolved in 873.6 g of dichloromethane (methylene chloride) was added, followed by. . .

DETD . . . solution of 0.5 g of thyrotropin-releasing hormone (TRH) in 0.2 g of water, a solution of 4.5 g of a **lactic acid** /glycolic acid copolymer [**lactic acid**/glycolic acid=75/25 (w/w), weight-average molecular weight: about 14000] in dichloromethane (4.9 ml) was added to yield a w/o emulsion.

DETD . . . gelatin were weighed and completely dissolved in 120 ml of water for injection. To this solution, 957.2 g of a **lactic acid**/glycolic acid copolymer [**lactic acid** /glycolic acid=75/25 (mol %), weight-average molecular weight: about 11,000] dissolved in 1602.8 g of dichloromethane was added, followed by stirring and. . .

DETD . . . gelatin were weighed and completely dissolved in 80 ml of water for injection. To this solution, 646.1 g of a **lactic acid**/glycolic acid copolymer [**lactic acid** /glycolic acid=75/25 (mol %), weight-average molecular weight: about 11,000] dissolved in 1081.9 g of dichloromethane was added, followed by stirring and. . .

CLM What is claimed is:

7. The method according to claim 1, wherein the biodegradable polymer is a **lactic acid**/glycolic acid polymer.

10. The method according to claim 7, wherein the composition ratio of a **lactic acid**/glycolic acid is from about 90/10 to about 50/50.

. . . than about 0.5 times/minute, wherein the physiologically active substance is leuprorelin or leuprorelin acetate, and the biodegradable polymer is a **lactic acid**/glycolic acid polymer having a composition ratio of about 90/10 to 50/50.

L1 ANSWER 13 OF 15 USPATFULL
AN 87:79766 USPATFULL
TI Treating states of agitation with azatetracyclic compounds
IN Blattner, Hans, Riehen, Switzerland
Storni, Angelo, Rheinfelden, Switzerland
PA Ciba-Geigy Corporation, Ardsley, NY, United States (U.S. corporation)
PI US 4707476 19871117
AI US 1980-191728 19800929 (6)
RLI Continuation of Ser. No. US 1978-961324, filed on 17 Nov 1978, now abandoned which is a continuation-in-part of Ser. No. US 1977-798204, filed on 18 May 1977, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Schwartz, Richard A.
LREP Glynn, Michael W., Fishman, Irving M.
CLMN Number of Claims: 15

ECL Exemplary Claim: 1,13
DRWN No Drawings
LN.CNT 1655
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Azatetracyclic compounds of the formula ##STR1## wherein the various substituents are defined hereinbelow. The novel compounds can be used as tranquillizing, antipsychotic and excitation-inhibiting compounds for the treatment of states of agitation. Specific embodiments are 3-methyl-2,3,4,5-tetrahydro-1H-dibenzo[2,3:6,7]thiepino[4,5-d]azepine and 3-methyl-2,3,4,5-tetrahydro-1H-dibenzo[2,3:6,7]oxepino[4,5-d]azepine.
SUMM . . . carboxylic and sulphonic acids, for example methanesulphonic acid, ethanesulphonic acid, 2-hydroxyethanesulphonic acid, acetic acid, malic acid, tartaric acid, citric acid, **lactic acid**, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, mandelic acid or embonic acid.
DETD thieno[2,3-b][1]**benzothiepine**-4,5-diacetoneitrile, m.p. 170.degree.-172.degree. C. (from acetonitrile), starting from 201 g (0.5 mole) of 4,5-bis-(bromomethyl)-thieno[2,3-b][1]**benzothiepine**;
DETD a mixture of 2-amino-4-bromo-1H-thieno[2',3':2,3][1]benzothiepino[4,5-d]azepine-hydrobromide and 4-amino-2-bromo-5H-thieno[2',3':2,3][1]benzothiepino[4,5-d]azepine hydrochloride as crude product, starting from 147 g (0.5 mole) of thienol[2,3-b][1]**benzothiepine**-4,5-diacetonitrile;

L1 ANSWER 14 OF 15 USPATFULL
AN 77:46672 USPATFULL
TI Heterocyclic S-imino-S-oxides
IN Dorhofer, Gunther, Allschwil, Switzerland
Heckendorn, Roland, Arlesheim, Switzerland
Schmid, Erich, Basel, Switzerland
Storni, Angelo, Rheinfelden, Switzerland
Zust, Armin, Birsfelden, Switzerland
PA Ciba-Geigy Corporation, Ardsley, NY, United States (U.S. corporation)
PI US 4045570 19770830
AI US 1975-575319 19750507 (5)
PRAI CH 1974-6423 19740510
DT Utility
FS Granted
EXNAM Primary Examiner: Jaisle, Cecilia M. S.
LREP Kolodny, Joseph G., Maitner, John J., Groeger, Theodore O.
CLMN Number of Claims: 14
ECL Exemplary Claim: 1,11,13
DRWN No Drawings
LN.CNT 970
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to new heterocyclic S-imino-S-oxides of the formula I ##STR1## in which one of the symbols X.sub.1 and X.sub.2 denotes a direct bond and the other denotes the vinylene group --CH=CH-- or the epithio radical --S--, Y.sub.1 and Y.sub.2 conjointly denote an additional bond or one of the symbols denotes hydrogen and the other denotes hydrogen or, conjointly with the symbol R.sub.1 or R.sub.2, which is present on the same carbon atom, denotes the oxo radical, one of the symbols R.sub.1 and R.sub.2 denotes hydrogen or lower alkyl and the other denotes hydrogen or lower alkyl or, conjointly with the symbol Y.sub.1 or Y.sub.2, which is present on the same carbon atom, denotes the oxo radical, or, if Y.sub.1 and Y.sub.2 conjointly denote an additional bond, also denotes lower alkoxy, and R.sub.3 and R.sub.4 independently of one another denote hydrogen, halogen up to atomic number 35, lower alkyl, lower alkoxy or trifluoromethyl and R.sub.5

denotes hydrogen or lower alkyl, and to their acid addition salts in particular the pharmaceutically with inorganic and organic acceptable acid addition salts. These new compounds possess valuable pharmacological properties. In particular they have an anticonvulsive activity and are useful for the treatment of epilepsy and of states of tension and states of agitation.

SUMM . . . Soc. 89, 5931 (1967)], 2-chloro-10,11-dimethyl-, 2-methoxy-10,11-dimethyl- and 2,10,11-trimethyl-dibenzo[b,f,] thiepine, (compare U.S. Pat. No. 3,636,045), 2-(trifluoromethyl)-10,11-dimethyl-dibenzo[b,f]thiepine, (compare U.S. Pat. No. 3,755,357), thieno[2,3-b][1]**benzothiepine** [compare M. Rajsner et al., Il Farmaco, Ed. Sci. 23, 140 (1968)] and 2-chlorothieno[2,3-b][1] **benzothiepine** [compare M. Rajsner et al., Collect. Czech. Chem. Commun. 35, 378-382 (1970)] as well as 4,5-dimethylthieno[2,3-b][1] **benzothiepine** and 9,10-dimethylthieno[3,2-b][1] **benzothiepine** [compare U.S. Pat. No. 3,682,959] .

SUMM . . . For example, hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, perchloric acid, methanesulphonic acid, ethanesulphonic acid, 2-hydroxyethanesulphonic acid, acetic acid, **lactic acid**, succinic acid, fumaric acid, maleic acid, malic acid, tartaric acid, citric acid, benzoic acid, salicyclic acid, phenylacetic acid, mandelic acid. . .

DETD . . . added dropwise at 30.degree. C. in the course of 10 minutes to a solution of 2.68 g (0.010 mol) of 10,10-dihydro-10-imino-thieno[2,3-b][1]**benzothiepine** hydrochloride in 75 ml of methanol and 40 ml of water. The reaction mixture is stirred for 4 days at. . . evaporated in vacuo. The residue is recrystallised from benzene with the addition of a little hexane. After drying, the resulting 10,10-dihydro-10-imino-thieno[2,3-b][1]**benzothiepine**-10-oxide melts at 143.degree.-145.degree. C.

DETD a. To manufacture the starting material, 8.1 g (0.037 mol) of thieno[2,3-b][1]**benzothiepine** are reacted with 9.6 g (0.044 mol) of O-mesitylenesulphonyl-hydroxylamine, analogously to Example 1a), 10,10-dihydro-10-imino-thieno [2,3-b][1]**benzothiepine** being obtained as an oil and being converted into the hydrochloride of melting point 205.degree. C (decomposition).

L1 ANSWER 15 OF 15 USPATFULL
AN 76:58494 USPATFULL
TI Aminoacyl compounds
IN Dorhofer, Gunther, Allschwil, Switzerland
Heckendorn, Roland, Arlesheim, Switzerland
Schmid, Erich, Basel, Switzerland
Storni, Angelo, Rheinfelden, Switzerland
Zust, Armin, Birsfelden, Switzerland
PA Ciba-Geigy Corporation, Ardsley, NY, United States (U.S. corporation)
PI US 3988467 19761026
AI US 1975-575320 19750507 (5)
PRAI CH 1974-6422 19740510
DT Utility
FS Granted
EXNAM Primary Examiner: Jiles, Henry R.; Assistant Examiner: Jaisle, Cecilia M. S.
LREP Kolodny, Joseph G., Maitner, John J., Groeger, Theodore O.
CLMN Number of Claims: 14
ECL Exemplary Claim: 1,13
DRWN No Drawings
LN.CNT 1278
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to new aminoacyl compounds of the formula I,

##SPC1##

SUMM . . . acids. For example, hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, perchloric acid, acid, methanesulphonic acid, ethanesulphonic acid, acetic acid, **lactic acid**, succinic acid, fumaric acid, maleic acid, malic acid, tartaric acid, citric acid, benzoic acid, salicylic acid, phenylacetic acid, mandelic acid. . .

DETD a. Analogously to Example 5 a), 10,10-dihydro-10-[N-(N,N-dimethylglycyl)-imino]-thieno[2,3-b][1]**benzothiepine** is obtained from 10.15 g (0.033 mol) of 10,10-dihydro-10-[N-(chloroacetyl)-imino]-thieno[2,3-b][1]**benzothiepine** and 3.4 g (0.073 mol) of dimethylamine.

DETD 10,10-Dihydro-10-[N-(chloroacetyl)-imino]-thieno[2,3-b][1]**benzothiepine**, which is employed as the starting product, can be prepared, for example, as follows:

DETD Analogously to Example 4 b), 10,10-dihydro-10-imino-thieno[2,3-b][1]**benzothiepine** is obtained as an oil from 8.1 g (0.037 mol) of thieno[2,3-b][1]**benzothiepine** and 9.6 g (0.044 mol) of O-mesitylenesulphonyl-hydroxylamine and is characterised as the hydrochloride; melting point 205.degree. C (decomposition).

DETD Analogously to Example 4 c), 10,10-dihydro-10-[N-(chloroacetyl)-imino]-thieno[2,3-b][1]**benzothiepine** is obtained from 11.1 g (0.0395 mol) of 10,10-dihydro-10-iminothieno[2,3-b][1]**benzothiepine** and 5.2 g (0.046 mol) of chloroacetyl chloride.

DETD . . . (0.165 mol) of a 15% strength methanolic methylamine solution, and 5,5-dihydro-5-[N-(N-methylglycyl)-imino]-10,11-dimethyl-dibenzo[b,f]thiepine is obtained from 10.15 g (0.033 mol) of 10,10-dihydro-10-[N-(chloroacetyl)-imino]-thieno[2,3-b][1]**benzothiepine** [compare Example 8 b) and c)] in 150 ml of benzene using the same amount of methylamine solution.